Interview #45

A total of 367 patients are registered with this center, but only half actually require regular treatment The others either do not treat except in emergency The age distribution of the patients is as follows

Less than 13 years	59
13 to 19 years	53
Over 20	249
Total	361

Their distribution by coagulation disorder is as follows

Hemophilia A	201
Hemophilia B	72
von Willebrand & Other blood disorders	73
Acquired hemophilia with inhibitors	15
Total	361

The product/patients mix among the active patients is as follows

DDAVP only	21	BeneFIX	40
Kogenate	26	Mononine	2
Recombinate	26	Total	42
Monarc-M	50		
Koate HP	10		
Total	133		

The PUPs are systematically prescribed a recombinant Factor VIII or Factor IX concentrate 36 patients have developed inhibitors Due to its unavailability in 1995, Konyne 80 is no longer used to treat patients with inhibitors Autoplex T, Feiba VH and NovoSeven are prescribed to them

No patients is on immune tolerance Seven inhibitor patients who were on IT lost their inhibitor (they were "tolerized") Approximately twenty patients are currently on secondary prophylaxis and four are on primary prophylaxis The prices charged to the patients by the treatment center are as follows

Product	Price to the Patient (per IU)	Product	Price to the Patient (per IU)
Bioclate	$ 0 92	BeneFIX	$ 0 92
Helixate	$ 0 92	Mononine	$ 1 00
Monarc-M	$ 0 49	Proplex T	$ 0 60
Monoclate P	$ 1 00		
Hemofil M	$ 0 84	Autoplex T	$ 1 09
Koate HP	$ 0.26	Feiba VH	$ 1 05
		NovoSeven *	$ 0.97
* Per mcg		Hyate C	$ 1 81

DDAVP (4mcg/ml, 40ml vial) is charged $222 to the patient (intravenous formulation) The spray costs $418 (1 5mg/mL)

Interview #46

This center treats 90 (+15 new patients) hemophilia A, 14 (+1) hemophilia B, and 10 von Willebrand's disease patients (+4) 60% of the patients are adult, and 40% pediatric The breakdown by severity follows

	severe	moderate	mild	total
Hemophilia A	43	15	32	90
Hemophilia B	6	6	2	14

Among the von Willebrand's disease patients, seven are type I, one type IIa, one type IIb and one type III The mild vWD patients use DDAVP, and the three severe use Humate P

All hemophilia A and B patients use recombinant product (none on plasma derived) The center writes a prescription for recombinant without brand name unless the patient asks specifically for one The home care companies fill the prescription based on product availability, assay cost and patient choice if requested Accordingly, the patient/product mix is currently estimated as follows

Recombinate	72	BeneFIX	14
Kogenate	9	Total	14
Bioclate	5		
Helixate	4		
Total	90		

Product shortage has not been a major concern for this center in 1999, except for getting particular vial sizes The acceptance of the second generation albumin-free rFVIII concentrates by the patients is unclear because they are not discussing it. As regards gene therapy, patients know a fair amount as it is discussed at the NHF chapter meetings Two guest speakers made presentations on this subject recently Patients, however, are "not jumping for it yet"

Eight patients have developed inhibitors All are high responders using Feiba VH or NovoSeven to control bleeds Six patients have tried immune tolerance - three successfully one partially successful, and two failed Ten patients are on primary prophylaxis, and ten on secondary prophylaxis

All patients use a home care company Most use Gentiva (Olsten), followed by Caremark, Apex, Bio Care, and New Factor

According to this respondent, the main issues facing patients today are

1) Continued access to a specialized center;
2) HIV, hepatitis C, and disease progression,
3) Drug resistance (inhibitors (?), and
4) Maintaining joint health

This respondent feels that all the manufacturers contribute equally to the community

Interview #47

This hemophilia treatment center serves 182 patients with Hemophilia A, 90 with Hemophilia B, 51 with von Willebrand's Disease, and 8 with other blood disorders

155 patients, or about 45%, are pediatric patients (under 19 years) including 12 who are less than 2 years old. This center has a higher than usual proportion of hemophilia B patients because a large family with Factor IX-deficient individuals lives in the area. Two patients with von Willebrand's disease control their bleeds with Alphanate, one of them had a reaction to Humate P Among the patients with "other bleeding disorders", two have Factor VII deficiency, and two have Factor XI deficiency Among the "active" hemophilia patients, the product mix is estimated as follows

Kogenate	40	BeneFIX	50
Recombinate	40	AlphaNine SD	[illegible]
Helixate	1	Mononine	[illegible]
Bioclate	1	Total	
Hemofil-M	55		
Monarc-M	20		
Total	157		

17 patients (13 pediatric, 4 adults) have developed inhibitors 12 patients, all pediatrics, are on immune tolerance Among the four adults, two use Feiba VH when they bleed, and two use NovoSeven Hyate C is mainly used for inhibitor patients undergoing surgery Three patients are on primary prophylaxis, and some 15 on secondary prophylaxis The latter number varies according to the needs

Close to 100 patients use Olsten (now "Gentiva"), almost 50 use HHS, some 20 use Caremark. Other home care companies serve another ten to fifteen patients

The treatment center buys factor concentrates from Gentiva under a consignment arrangement at the prices shown below

Product	Acquisition Price
Kogenate	$ 0 69
Recombinate	$ 0 73
Helixate	$ 0 70
Bioclate	$ 0 74
Monarc-M	$ 0 36
Hemofil-M	$ 0 48
Monoclate P	$ 0 53
Alphanate	$ 0 42
Koate DVI	$ 0 33
Profilate OSD *	$ 0 20
BeneFIX	$ 0 79
AlphaNine SD	$ 0 62
Mononine	$ 0 77
Bebulin VH	$ 0 27
Konyne 80	$ 0 26
Proplex T	$ 0 19
Profilnine SD	$ 0 26
Feiba VH	$ 0 89
Autoplex T	$ 0 77
Hyate C	$ 1 36
NovoSeven	$ 0 91

The clotting factors are purchased through a close bid tender, with a one year renewable contract.

* No longer manufactured

Interview #48
The hemophilia patient population of this center is as shown below

	Severe	Moderate	Mild	Total
Hemophilia A	11	5	25	41
Hemophilia B	5	3	10	18
Total				59

All the patients are adults or teenagers, the youngest one is 16 years old In addition to the hemophilia patients, 39 von Willebrand's disease patients are registered at this center, all type I except two type IIb These severe vWD patients all use Humate P

33 hemophilia patients do not need any regular treatment, and one Factor VIII-deficient carrier uses Recombinate There is no patient with inhibitors to Factor VIII or IX The product/patients mix among those on home treatment is as follows

Hemofil M	3	BeneFIX	5
Monoclate P	1	Mononine	1
Kogenate	1	Sub-total	6
Helixate	2		
Recombinate	7		
Total	14		

The shortage of Alpha's and Centeon's products has compelled the patients to switch to Hemofil M and BeneFIX . A small number of them has remained on the Centeon's products which were sporadically available
Two patients are currently on secondary prophylaxis, none is on primary prophylaxis

20 patients are on home infusion 2 are affiliated with Caremark, 6 with Olsten ("Genuva") one with HHS, 10 with the university home care program which has increased its membership impressively, from one patient last year to ten Finally, one patient is still affiliated with NMC which is less focused on hemophilia than the others although its services are reported to be adequate and one patient gets its clotting factors from Chronimed.

The treatment center staff has attended a training session about gene therapy, and conveyed some of the information to the patients Five of them asked about this new treatment modality and they are believed to consider it if it is safe and effective

Interview #49
The following acquisition prices apply to this hospital in January 2000 It is affiliated to the Novation GPO

Product	Acquisition Price per IU	Product	Acquisition Price per IU
Bioclate	$ 0 73	BeneFIX	$ 0 75
Helixate	$ 0 68	AlphaNine SD	$ 0 60
Kogenate	$ 0 78	Profilnine SD	$ 0 40
Recombinate	$ 0 77	Proplex T	$ 0 21
Alphanate	$ 0 40	Bebulin VH	$ 0 25
Koate HP	$ 0 39		
Hyate C	$ 1 83	Autoplex T	$ 0 52
Humate P	$ 0 96	Feiba VH	$ 0 89

Interview #50
During the 1999 fiscal year, this State Pharmacy dispensed approximately

- 572,000 units of recombinant Factor VIII,
- 3.1 million units of monoclonal antibodies-purified Factor VIII,
- 57,000 units of intermediate purity Factor VIII,
- 629,600 units of recombinant Factor IX,
- One million units of "pure" Factor IX,
- 495,000 units of PCC, and
- 315,000 units of Activated Factor IX Complex

The following prices (per international unit) applied

Product	Acquisition Price per International Unit
Kogenate	$ 0 61
Recombinate	$ 0 64
Bioclate	$ 0 60

Product	Acquisition Price per International Unit
Monarc-M	$ 0 32
Monoclate P	$ 0 45
Hemofil M	$ 0 36
Alphanate	$ 0 34
BeneFIX	$ 0 66
AlphaNine SD	$ 0 54
Mononine	$ 0 63
Profilnine	$ 0 18
Proplex T	$ 0 15
Bebulin VH	$ 0 22
Feiba VH	$ 0 70
Autoplex T	$0 63

Interview #51

49 hemophilia A patients are treated at this center, 13 hemophilia B 43 with von Willebrand's disease and 8 persons with other blood disorders (platelet dysfunction, etc) 77 patients are less than 19 years old, 20 over 19

All the hemophilia patients (A or B) use a recombinant concentrate However, one hemophilia A patient with an inhibitor uses Feiba VH The patient/product mix is estimated as follows

Kogenate/Helixate	32	BeneFIX	13
Recombinate/Bioclate	17	Total	13
Total	49		

The reason Kogenate/Helixate is primarily used at this center is historical, as it was involved in the Kogenate pre-licensure clinical trial, and the patients had no reason to change product once it was approved by the FDA

Two patients with inhibitors are on immune tolerance, one of them occasionally needs NovoSeven Another inhibitor patient uses Feiba VH Two patients who had an inhibitor have lost it One is on maintenance, the other one, on demand

ReFacto will not bring any significant safety enhancement, as the presence of albumin in recombinant Factor VIII has not been an issue at this center The choice will be offered to the patients, but no one has indicated that he would switch when the product becomes available The question of the chromogenic assay to measure the Factor VIII level may be a slight problem initially but with practice, the treating staff will soon be able to use it as easily as the current Factor VIII level testing It is believed that accuracy of the test will not be a problem

Almost every one of the hemophilia B patients get a higher dosage of BeneFIX than is indicated on the package insert, +50% instead of +20%

Some 6 vWD patients need Factor replacement on a regular basis, all Type IIb or III, and one peculiar Type I who bleeds frequently

Some two or three patients are on primary prophylaxis, defined at this center as the appearance of a frequent bleeding pattern The regimen is an infusion every other day to maintain the Factor VIII at 2% of the normal level For hemophilia B, the frequency is three times a week, to maintain the patient at 1% of the normal Factor VIII In a prophylaxis regimen, the frequency of the infusion of Factor VIII is higher than the frequency of Factor IX infusions because Factor VIII has a 8 to 12 hours half life whereas the half life of Factor IX, including BeneFIX, is 18 to 24 hours This is

different from the recovery which gives a 2% increase in the Factor VIII level for each international unit infused while the increase for Factor IX is 1% per IU infused, and 0 8% for BeneFIX. hence the need to infuse more of it

Gene therapy is considered promising a patients are generally keen to know more about it. They realize that it is still at least five years away

Interview #52
On average, Dr D cares for five hemophilia patients with inhibitors, three hemophilia A and two hemophilia B

1) When a "significant" bleed occurs in a hemophilia patient with an inhibitor Dr D typically follows the treatment algorithm designed by an organization to which he belongs The algorithm starts with the infusion of a PCC If the bleeds does not stop, an aPCC (Feiba VH or Autoplex T) is used In case of life-threatening bleed, porcine Factor VIII or rFVIIa is prescribed [provided the conditions for the compassionate use are met] "No aPCC is used in life-threatening situations"

2) The inhibitor level determines the dosage It varies according to the product as well The range is quite wide, from 50 to 200 IUs per Kg bodyweight, typically 100 IUs per Kg for an aPCC A number of tests (BU level, etc) are performed before deciding on a dosage [provided there is no life-threatening urgency]

   Note according to a different source, the dosage used with Autoplex T ranges from 25 to 100 IUs per Kg bodyweight On average, 75 IUs are usually prescribed for a joint bleed Two infusions are generally enough to control the bleed The dosage used with Feiba VH is about the same (65 corrections units per Kg bodyweight) With NovoSeven as many as eleven infusions are reportedly needed to accomplish the same result The typical dosage with NovoSeven is 80mcg/Kg bodyweight

   Massive infusions of factor VIII or IX can accomplish a good result when the product is infused in continuous infusion because the timing factor plays an important role in the treatment

   Dr D does not know the price of each product but realizes that the cost of treating an inhibitor can run to $2,000 per day (including immune tolerance), and that it is much cheaper when a PCC is used

3) In case of hemarthrosis, PCC and aPCC are successful in 50% of the cases, and human albumin in 25% of the cases (control group) A paper published in the 1980 s compared PCC and Feiba, and concluded that there was no major difference in treatment outcome According to Dr D , NovoSeven is efficacious in 90% of the cases, and it could easily become the product of choice in the treatment of inhibitors

4) From the cost viewpoint, as mentioned earlier, the basic distinction is between "PCC" and "aPCC" Once the option "PCC" has been exhausted, the treating physician knows that he/she enters the land of the expensive products In case of life threatening bleed, the cost of product does not play any role

5) To the extent possible, elective surgery is avoided in hemophilia patients with an inhibitor If surgery must be performed - usually in some kind of emergency - all precautions are taken to avoid a bleeding accident First a massive dose of Factor VIII or IX is infused in the patient's system, then all the tests are made (recovery and half-life, etc), and appropriate safeguards are established, such the immediate availability of Autoplex T, Feiba VH or NovoSeven (or porcine Factor VIII)

6) Insurance companies do not have the faintest idea about hemophilia care [Since many doctors including many hematologists (said Dr D) are often incompetent when faced with a serious

hemophilia case, it is not surprising - and quite understandable that insurers are ignorant about it, too] The attitude of insurance companies is clear either they pay or they don't Fortunately, Dr D and his patients have never been denied payment for inhibitor treatment in hemophilia No question has ever been asked by the insurance companies until now Dr D points out that the insurance companies would only cover (or strongly recommend) the exclusive use of PCC if they knew that it cost so much less than all the other products!

7) The rationale for the plasmapheresis/Protein A column approach is that a lowered IGG level (obtained through plasmapheresis) would increase the chances of a successful tolerization through immune tolerance Dr D does not believe that "one follows the other", or that the immune tolerance will necessarily be successful because the IGG level is low The fact that this procedure has apparently been used with success in Scandinavia for many years is not convincing, as "there may be other factors"

ANNEXES

a) Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) Recommendation #95, November 1999

b) NHF, Community Alert'99. Vol. 6, November 1999 (extract) "Frequently asked questions about Gene Therapy", page 1-3

c) Centers of Disease Control (CDC) Report on the Universal Data Collection System (UDC), Janaury 2000, Vol 2, No 1

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Recommendation # 95

MEDICAL AND SCIENTIFIC ADVISORY COUNCIL RECOMMENDATIONS CONCERNING THE TREATMENT OF HEMOPHILIA AND RELATED BLEEDING DISORDERS

(Revised November 1999)

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) on November 6, 1999, and adopted by the NHF Board of Directors on December 21, 1999

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116 West 32nd Street 11th Floor
New York, NY 10001
(800) 42-HANDI (212) 328-3700 fax (212) 328 3777
www.hemophilia.org info@hemophilia.org

Founded 1948

I. Recommendations for Physicians Treating Patients with Hemophilia A and B, von Willebrand Disease, and other Congenital Bleeding Disorders

A. Treatment of Hemophilia A

1 Patients Who Are HIV Seronegative - Factor VIII Products

a. Recombinant Factor VIII

Recombinant (r) FVIII, produced by well-established hamster cell lines that have been transfected with a gene for human FVIII, is stabilized in human albumin. The risk of human viral contamination is definitely much lower than for plasma-derived FVIII products. No seroconversions have been reported with any of the currently available products, thus recombinant factor VIII products are the recommended treatment of choice especially for young and newly diagnosed patients who have not previously received any blood or plasma-derived products (Table IA)

b Viral Safety and Plasma-Derived Factor VIII Products

Improved viral-depleting processes and donor screening practices have resulted in FVIII products with greatly reduced risk for transmission of human immunodeficiency virus and hepatitis B and C. No seroconversions to HIV, HBV, or HCV have been reported with any of the FVIII products currently marketed in the United States, including products that are heated in aqueous solution (pasteurized), solvent-detergent treated, and or immunoaffinity purified. Thus, each of these methods appears to have greatly reduced the risk of viral transmission compared with older methods of viral inactivation (1-3). There remains the *possibility* of HIV-1, HIV-2, or hepatitis B or C virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. It is known that the non-lipid enveloped viruses human parvovirus B19 and hepatitis A virus can still be transmitted (16,18), although additional steps such as viral filtration are being added to reduce these risks as well (Table IB)

2 Patients Who Are HIV Seropositive - Cellular Immunity and Factor VIII Products

Emerging data suggest the possible superiority of immunoaffinity purified FVIII concentrates over products of intermediate purity for the maintenance of cellular immunity in HIV-infected persons (19). Therefore, it is recommended that physicians should carefully consider such information when selecting products for use in HIV-infected persons with hemophilia.

Recombinant FVIII products and products of high purity produced by methods other than immunoaffinity have yet to be directly compared with intermediate purity products to determine if they are similarly beneficial

3 Cryoprecipitate Not Recommended

Methods of viral inactivation (pasteurization, solvent-detergent treatment, immunoaffinity purification) have resulted in a reduced risk of HIV and hepatitis B and C transmission with plasma-derived factor VIII concentrates (2, 3, 5-7) Moreover, FVIII products manufactured by recombinant technology which theoretically do not transmit human viruses are now licensed

For these reasons, cryoprecipitate should not be used as a treatment alternative Despite donor screening for antibody to HIV-1, HIV-2, and hepatitis C virus (HCV) and for hepatitis B surface antigen (HBsAg), cryoprecipitate might still be infectious for several reasons including the potential for several months' delay in seroconversion after HIV or HCV infection While the current estimate for the risk of HIV infection from a single unit of blood is one in every 450,000 to 660,000 transfusions (20), the risk of HCV transmission is somewhat higher being approximately 3 in 10,000 (21)

B Treatment of Hemophilia B

1 Patients Who are HIV Seronegative - Human Immunodeficiency Virus (HIV) and Factor IX Products

a. Recombinant Factor IX

Recombinant factor IX is produced in Chinese hamster ovary cells, no human plasma products are used in its manufacturing process Thus the risk of human blood-borne viral contamination is essentially zero (23) Recombinant factor IX is considered to be the treatment of choice for young and newly diagnosed patients (Table IIA)

b Viral Safety and Plasma-Derived Factor IX Products

Improved viral depleting processes and donor screening practices have resulted in FIX products with greatly reduced risk for HIV and hepatitis B and C transmission (4) Viral attenuation methods used in the production of licensed FIX products that appear to be effective for reducing the risk of hepatitis are dry heating at 80°C for 72 hours, solvent-detergent treatment, vapor treatment, and sodium thiocyanate plus ultrafiltration Purification steps involved in the preparation of coagulation FIX products are associated with loss of several additional logs of virus There remains the slight possibility of viral transmission with the currently marketed viral-inactivated, plasma-derived products Transmission of human parvovirus B19 and hepatitis A virus through the use of these products has been documented, but the risk has been reduced with additional viral attenuation methods (Table IIB)

2 Patients Who Are HIV Seropositive - Cellular Immunity and Factor IX Products

Studies of immune function in HIV-seropositive patients with hemophilia B similar to those described for patients with hemophilia A (Section A 2 , above) have not been reported However, since studies have shown improved immune function in patients receiving high purity factor VIII products, extrapolation suggests that HIV-seropositive hemophilia B patients should also be treated with high purity products (immunoaffinity purified recombinant

3 Reduction of Thromboembolic Risk During Surgery

The use of coagulation FIX concentrates or recombinant factor IX rather than prothrombin complex concentrates is recommended in certain situations associated with a higher risk of thromboembolic complications such as surgery or severe hemorrhage requiring treatment 2-3 times per day (see MASAC Statement Regarding the Use of Coagulation Factor IX Products in Persons with Hemophilia B, May 29, 1992)

C Treatment of Mild Hemophilia A

Desmopressin (DDAVP injection or Stimate nasal spray) should be used whenever possible for patients with mild hemophilia A DDAVP is now licensed and available in both parenteral and highly concentrated intranasal spray formulations (Table IV) When desmopressin does not provide adequate treatment, these patients should be treated as per section A above

D Treatment of von Willebrand Disease (vWD)

Most persons with von Willebrand disease type 1 are most appropriately treated with desmopressin (DDAVP injection or Stimate nasal spray), given either parenterally or by highly concentrated nasal spray (Table IV) Some Type 2A patients may respond to DDAVP, clinical trials should be done to determine whether DDAVP or factor VIII concentrate should be used for these patients If judged necessary (e g , Type 2B vWD, Type 3 vWD, and Type 1 or 2A vWD who have become transiently unresponsive to DDAVP or with surgical situations, especially in young patients virus-inactivated FVIII preparations rich in von Willebrand factor (e g , Alphanate, Humate-P Koate DVI) are recommended (9-13) (Table IC)

Cryoprecipitate should not be used except in life and limb-threatening emergencies when factor concentrate is not immediately available Plas+SD does not contain good von Willebrand factor multimers so it should not be made into cryoprecipitate

E Treatment of Patients with Inhibitors to Factors VIII and IX

1 Recombinant Factor VIIa

Recombinant factor VIIa (NovoSeven) has recently been licensed for use in patients with inhibitors to factor VIII or IX It is produced by baby hamster kidney cells No human albumin or other proteins are used in the production of NovoSeven It is not stabilized with albumin Thus the risk of transmission of human viruses is essentially zero (Table IC)

2 Porcine Factor VIII

Porcine factor VIII can be used in patients with inhibitors to human factor VIII Porcine factor VIII (Hyate C) is obtained from a colony of carefully maintained pigs which are screened frequently for any viruses There has been no documented transmission of porcine viruses especially porcine parvovirus, to individuals who have been treated with this product (Table ID)

3 Activated Prothrombin Complex Concentrates

These products contain activated factors IIa, VIIa, and Xa. These factors are able to bypass an inhibitor to factor VIII or factor IX and promote hemostasis These products are derived from human plasma but are treated with dry heat and/or vapor (steam) heat to eliminate viruses (Table IID)

F Treatment of Patients with Rare Congenital Bleeding Disorders

1 Recombinant Factor VIIa

Recombinant factor VIIa (NovoSeven) has recently been licensed in the United States It is produced by baby hamster kidney cells, no human albumin is used in its production or formulation It can be used to treat patients with congenital factor VII deficiency (Table III)

2 Prothrombin Complex Concentrates

Plasma-derived prothrombin complex concentrates (PCCs) can be used to treat patients with deficiencies of factors II, VII, and X It should be noted, however, that these products vary considerably in the amounts of these factors that they contain. Not only is there a marked difference in factor content between the different commercial preparations, but factor content varies between lots produced by the same manufacturer (Table IIC)

3 Fresh Frozen Plasma

Fresh frozen plasma (FFP) can be used to treat patients with mild deficiencies of any of the clotting factors for which specific clotting factor concentrates are not available Two types of FFP are available which have been processed so as to reduce the risk of viral transmission (Table V)

a. Donor retested FFP is produced from single units of plasma, the donor must come back and test negative on a second donation in order for the first donation to be released. This product is available from some community blood centers but not the American Red Cross (ARC)

b Plas+SD is produced from single units of FFP that are pooled in lots of 2500 units and treated with solvent detergent to kill HIV, hepatitis B, and hepatitis C This method does not kill hepatitis A or parvovirus However, nucleic acid testing has reduced the risk of transmission of these two viruses to essentially zero The FFP is collected by ARC processed by Vitex, and then distributed by ARC

4. Fibrogammin P is a plasma-derived factor XIII concentrate for treatment of factor XIII deficiency It is not yet licensed in the United States but is available under an Investigational New Drug (IND) protocol

G Vaccination for Hepatitis A and B

1. Hepatitis B vaccine is recommended for all children by the American Academy of Pediatrics In persons with hemophilia and other congenital bleeding disorders, this immunization is particularly important and should be started at birth or at the time of diagnosis Primary immune response should be documented

2 Hepatitis A vaccine is recommended for all individuals 2 years of age and older with hemophilia and other congenital bleeding disorders who are HAV seronegative [4 5]

H Other Issues of Importance

1. Need for Continued Collection and Reassessment of Data

When choosing the appropriate products for their patients with hemophilia physicians will need to continue to exercise their best judgment based on their assessment of emerging data The data concerning the effectiveness of different viral-depleting processes are based on a relatively small number of published studies, most involving small numbers of previously untreated subjects (8) Additional data are essential to provide for a better understanding about the safety of blood products If a previously seronegative patient seroconverts to any blood-borne virus, this should be immediately reported to the FDA, to the manufacturer of the product received, and to the CDC

2 MASAC recommends continued viral safety studies of all licensed products and maintenance of a serum bank to enable quick evaluation of possible transmission of viral infection by such products

3 Decisions about the selection of products for treatment of hemophilia are complicated for patients, families, and treating physicians Thus, patient education, psychosocial support and financial counseling are critical components of comprehensive care regardless of a patient's HIV status

4. Patients should enroll in a voluntary notification system in order to be notified promptly of any recalls of factor products they may be using

III. Recommendations to Manufacturers of Coagulation Product

A We recommend continued vigilance in donor screening and donor testing at blood and plasma collection facilities

1 Plasma must not be collected from donor centers that draw from population groups in which there is a relatively high incidence of hepatitis and AIDS
2 Manufacturers should disclose the incidence of hepatitis and HIV infection at individual plasma centers Maximum allowable viral marker rates for the donor population for anti-HCV, anti-HIV, and HBsAg should be established
3 Manufacturers should use only plasma that is collected by facilities qualified to receive the Quality Plasma Program (QPP) certification by the American Blood Resources Association in accordance with recommendations to hemophilia treatment centers (see "MASAC Resolution on the Quality Plasma Program," December 3, 1992, Medical Bulletin #168, Chapter Advisory #170)
4 Plasma should not be accepted for further processing until the donor has successfully passed at least two health history interviews and screening tests within a specified time period
5 All donations should be held for at least 60 days If during this period the donor seroconverts and tests positive for a virus, or is otherwise disqualified, the held donation should be destroyed
6 Donors diagnosed with CJD or at risk for CJD should continue to be deferred from donating blood and plasma. If such individuals are identified after donation, all products containing their plasma, including albumin used as an excipient (stabilizer) in plasma-derived and recombinant products, should continue to be quarantined, and if marketed, withdrawn

B Increased efforts should be made to exclude from further processing the plasma from donors who are infected with HIV, HBV, HAV, HCV, human parvovirus, and CJD

1 Tests to identify viral nucleic acids (e g , polymerase chain reaction [PCR] and other genome amplification tests) should be implemented expediently for all plasma that will be further processed
2 Priority of test implementation should focus on viral agents that are not inactivated by current viral elimination techniques, namely, parvovirus B19 and HAV
3 To further identify donors who are infected and donate during the window period, viral nucleic acid testing should be implemented for HCV, HIV, and HBV
4 These tests, once implemented, should offer significant incremental sensitivity over the HIV antigen test and serologic tests for HIV, HCV, and HBV. This can best be accomplished by testing individual donors or very small donor mini-pools
5 Infected donors should be notified of their status in an appropriate manner
6 Efforts to develop a test to identify donors potentially infectious for CJD and related agents should be given high priority.

C Plasma pools should be decreased in size to levels approaching 15,000 donors per lot of finished product

1 Reduction in the number of donors in final lots of product will decrease the spread of a new infectious threat that is transmitted via plasma products
2 Manufacturers should disclose the number of donors in each lot of their products

3 Albumin used as an excipient in purified coagulation products should be obtained from the same plasma pool to eliminate further exposure to donors
4 Reduction in the number of donors in final lots of product will decrease the amount of product withdrawn or quarantined as a result of identification of a donor with a potential transmittable disease (e g , CJD)

D. Improved viral inactivation and elimination are required in coagulation products

1 All efforts should be made to remove human albumin from recombinant factor VIII products
2. Increased efforts should be made to eliminate human and bovine proteins from the manufacturing process of recombinant factor VIII products
3 Inactivation of non-lipid enveloped viruses (e g , human parvovirus B19 HAV) is inadequate with existing techniques New methods must be identified to minimize the chance of transmitting these and similar agents which may emerge in the blood supply
4 Research to identify methods to eliminate the infectivity of the CJD agent and similar prion agents that may appear in the blood supply (e g , Mad Cow Disease) is urgently needed

E. Reporting of adverse events associated with coagulation products should occur more expeditiously

1 Manufacturers should report suspected viral transmission events to the FDA monthly
2 Manufacturers should cooperate fully with the FDA and CDC in their investigations to determine if their product is responsible for a viral infection
3 New products are often approved with small numbers of patients evaluated in clinical trials Manufacturers are strongly encouraged to conduct Phase IV post-licensure studies for efficacy, surveillance for viral infections
4 The FDA is bringing standards for the manufacture of coagulation products up to the level of other drugs regulated by the FDA Manufacturers should anticipate that the FDA is seeking enhanced training programs, manufacturing controls, quality assurance, and quality control and promptly take necessary steps to bring their facilities into compliance, if they have not already done so

F Notification to consumers and their health care providers of safety and regulatory problems must occur in a more expeditious fashion

1 Manufacturers are responsible for notifying their customers The FDA has defined the customer as the "end-user" of the product namely, the person with a coagulation disorder and their healthcare provider Manufacturers should accept the responsibility for notifying their customers if they have purchased a product that is out of compliance
2 Notification to customers must occur early in the investigation While we recognize that occasionally a product may be exonerated from disease transmission, it is vital to err on the side of safety and remove a product under investigation from its point of use including patients' homes
3 While the voluntary notification system implemented by some companies will go a long way toward putting a system into place, it should not be considered a substitute for the responsibility of the manufacturers have to notify their customers directly
4 Intermediaries, including home care companies, must keep accurate records of the lots their customers use and have systems in place to notify patients and their healthcare providers immediately upon learning of a compromised product lot

G Research and development of improved coagulation products that would expedite the transition to total prophylaxis for all persons with coagulation disorders are strongly encouraged.

1 Licensed and improved products to treat patients with von Willebrand disease and patients with inhibitors are urgently needed
2 Recombinant products that could be taken less frequently or administered other than intravenously would be of tremendous benefit to individuals on prophylaxis regimens
3 Methods to manufacture coagulation products more inexpensively, such as use of transgenic animals, would increase supply and availability worldwide
4 Costs of coagulation products should be reduced
5 NHF has endorsed the development of clinical trials in gene therapy to cure bleeding disorders Manufacturers should facilitate the clinical development of this technology

III. Recommendations to the Food and Drug Administration

The Food and Drug Administration is responsible for regulating the manufacturers of coagulation products to ensure that licensed products are safe and effective Many of our recommendations for manufacturers should be regulated proactively by the FDA

A The FDA should establish stricter guidelines for the collection of plasma, to include the use of plasma from repeat donors only, inventory hold, establishment and publication of viral marker rate standards at plasma collection centers, and establishment of sensitive genome amplification tests

B The FDA should implement pool size restrictions along the lines of their proposal in 1996 of 15,000 donors for source plasma

C Research to identify improved inactivation and elimination techniques for non-lipid enveloped viruses should be actively encouraged by the FDA A timetable for implementation of these techniques for all coagulation products should be established with a goal for implementation by 2000

D Validation studies to identify the amount of removal of the CJD agent should be recommended by the FDA to each manufacturer for each of their products

E The FDA should work with the National Heart, Lung, and Blood Institute and industry to ensure that sufficient resources are available to develop inactivation techniques for all CJD-related agents

F The FDA should maintain sufficient compliance checks to ensure that manufacturers are expeditiously reporting any and all suspected infectious diseases associated with coagulation products

G The FDA should work with the CDC to investigate any suspected viral transmission via coagulation factors Patients and providers should be included as advisors in the early stages of each investigation to provide relevant perspectives

H Products under investigation should be assumed to be implicated in viral transmission until proven otherwise and NOT assumed to be safe until proven to transmit a virus Accordingly, these products should be removed from the distribution path, including removing them from patients' homes

I The FDA has the authority to regulate a mandatory notification system that follows the product through its entire distribution pathway The FDA should enforce the implementation and maintenance of such a system

J The FDA should continue to bring the coagulation products industry in line with good manufacturing practices of pharmaceutical companies that manufacture other classes of drugs

K All products offering incremental safety and efficacy advantages to the bleeding disorders community should have expedited regulatory review

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GLOSSARY TO MASAC RECOMMENDATIONS

Activated Prothrombin Complex Concentrates

Two prothrombin complex concentrates are purposely "activated" so that they contain some FIX, FX, etc in active form (FIXa, FXa, etc) Autoplex T and FEIBA are to be used in inhibitor patients only!

Coagulation Factor IX Concentrate

Factor IX products which contain very little or no coagulation factors other than FIX include AlphaNine SD and Mononine

Desmopressin (DDAVP, Stimate)

Desmopressin acetate is a synthetic analogue of the natural pituitary antidiuretic hormone, 8-arginine vasopressin When given to persons who have the capability of producing some FVIII or vWF, the drug effects a rapid, transient increase in FVIII and vWF It can be given intravenously, subcutaneously, or by intranasal spray The intranasal spray form is called Stimate Nasal Spray

Dry Heat Treated

No currently available FVIII products are exclusively dry heat-treated Currently available FIX products that are dry heat-treated include Proplex T and Konyne 80 Proplex T is dry-heated at 60°C for 144 hours Konyne 80 is heated at 80°C for 72 hours

Factor VIII Products Rich in von Willebrand Factor

In certain of the plasma-derived intermediate purity FVIII concentrates the hemostatically important high molecular weight multimers of von Willebrand factor are preserved These include Alphanate, Humate-P, and Koate DVI They have often proved effective in preventing or controlling bleeding in persons with vWD Humate-P has been approved by the FDA for use in patients with von Willebrand disease

There is also a vWF product manufactured in France that is currently in U S clinical trials sponsored by the American Red Cross

Heated in Aqueous Solution (Pasteurized)

Factor VIII concentrates that are heated for 10 hours at 60°C in aqueous solution in the presence of stabilizers such as sucrose or neutral amino acids Products include Humate-P and Monoclate P

Immunoaffinity Purified

Factor VIII or FIX concentrates that are purified using murine monoclonal antibodies attached to an affinity matrix Viral attenuation is augmented before immunoaffinity purification by pasteurization (Monoclate P) or by detergent-solvent treatment (Hemofil M and Monarc-M) In the case of Mononine (a coagulation FIX product), viral attenuation is augmented by sodium thiocyanate and ultrafiltration

Prothrombin Complex Concentrate

Prothrombin complex concentrate (PCC) contains factors II, VII, IX, and X and proteins C and S (plus small amounts of activated coagulation factors) Examples of these products include Bebulin VH Konyne 80, Profilnine SD, and Proplex T

Recombinant Factor

Recombinant (r) FVIII refers to genetically engineered or cloned FVIII that is not derived from human or animal plasma. The gene encoding normal human FVIII is inserted into hamster cell nuclei (cells obtained from well-established baby hamster kidney cell lines or Chinese hamster ovary cells) The hamster cells then produce FVIII that is indistinguishable from plasma-derived human FVIII Currently licensed rFVIII products are Recombinate and Kogenate Recombinate is also distributed under the trade name Bioclate and Kogenate is distributed as well under the name Helixate These products are stabilized with human albumin that has been heat-treated.

A recombinant FIX (rFIX) product, BeneFIX, has also been licensed. The rFIX is produced by Chinese hamster ovary cells It contains no albumin stabilizer

A recombinant factor VIIa product (NovoSeven) has recently been licensed in the United States The rFVIIa is produced by baby hamster kidney cells No human serum proteins are used in its production or formulation

Another rFVIII product, a deletion rFVIII product that lacks the B domain and contains no albumin stabilizer, has been in pre-licensure clinical trials in Europe since March 1993 Pre-licensure clinical trials began in the United States in 1995

Solvent Detergent Treated

Factor VIII concentrates that are manufactured using combinations of the solvent, Tri(n-Butyl) Phosphate (TNBP), with a detergent, such as cholate, Tween 80 (polysorbate), or Triton-X-100, to inactivate lipid-enveloped potential viral contaminants (lipid-enveloped viruses include HIV HBV HCV) Alphanate and Koate DVI are solvent-detergent treated using TNBP and Polysorbate 80 Hemofil M and Monarc-M are solvent-detergent treated with TNBP and Triton X-100 A coagulation FIX product (AlphaNine SD is solvent-detergent treated using TNBP and Polysorbate 80, as is the prothrombin complex concentrate Profilnine SD

Vapor Treated

Two coagulation products currently licensed in the U S use vapor (steam) treatment for viral attenuation. Bebulin, a FIX complex concentrate, and FEIBA VH, an activated prothrombin complex concentrate are both vapor treated for 10 hours at 60°C and 1190 mbar pressure, followed by 1 hour at 80°C under 1375 mbar pressure

TABLE I. FACTOR VIII PRODUCTS LICENSED IN THE U.S.

A. RECOMBINANT FACTOR VIII PRODUCTS

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Specific Activity of Final Product (IU/mg protein)	Specific Activity Discounting Albumin (IU/mg protein)	Hepatitis Safety Studies in Humans with this Product
Bioclate	Baxter Hyland Immuno (distributed by Aventis Behring)	1 immunoaffinity chromatography	1 65-19	> 3,000	Yes
Helixate	Bayer (distributed by Aventis Behring)	1 immunoaffinity chromatography	8-30	> 3,000	Yes
Kogenate	Bayer	1 immunoaffinity chromatography	8-30	> 3,000	Yes
Recombinate	Baxter Hyland Immuno	1 immunoaffinity chromatography	1 65-19	> 3,000	Yes

TABLE I. FACTOR VIII PRODUCTS LICENSED IN THE U.S. (Continued)

B IMMUNOAFFINITY PURIFIED FACTOR VIII PRODUCTS DERIVED FROM HUMAN PLASMA

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity of Final Product (IU/mg protein)	Specific Activity Discounting Albumin (IU/mg protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
Hemofil M	Baxter Hyland Immuno (BHI)	1 immunoaffinity chromatography 2 solvent detergent (TNBP/Triton X-100)	2-11	> 3,000	Yes (3)	No
Monarc M	Manufactured by BHI for American Red Cross (ARC) from ARC-collected plasma (distributed by ARC)	1. immunoaffinity chromatography 2 solvent detergent (TNBP/Triton X-100)	2-11	> 3,000	No	Yes (3)
Monoclate P	Aventis Behring	1 immunoaffinity chromatography 2 pasteurization (60°C, 10h)	5-10	> 3,000	Yes	Yes

TABLE I. FACTOR VIII PRODUCTS LICENSED IN THE U.S. (Continued)

C. FACTOR VIII PRODUCTS DERIVED FROM HUMAN PLASMA THAT CONTAIN VON WILLEBRAND FACTOR

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity of Final Product (IU Factor VIII/mg protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Method	FDA Approved for von Willebrand Disease
Alphanate	Alpha	1 affinity chromatography 2 solvent detergent (TNBP and polysorbate 80) 3 heat (80°C, 72h)	8-30	No	Yes	No
Humate-P	Aventis Behring GmbH (Marberg, Germany)	1 pasteurization (60°C, 10 hrs)	1-2	Yes (2)	No	Yes
Koate-DVI	Bayer	1 solvent detergent (TNBP and polysorbate 80) 2 heat (80°C, 72h)	9-22	No	Yes	No

TABLE I. FACTOR VIII PRODUCTS LICENSED IN THE U.S. (Continued)

D. PORCINE FACTOR VIII PRODUCTS
(FOR USE IN PATIENTS WITH INHIBITORS TO HUMAN FACTOR VIII)

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity of Final Product (IU/mg protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Method
Hyate C	Speywood (Wales)	None (but no report of transmission of any viruses to humans)	>50	No	No

TABLE II. FACTOR IX PRODUCTS LICENSED IN THE U.S.

A. RECOMBINANT FACTOR IX PRODUCTS

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Contains human plasma proteins?	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
BeneFIX	Genetics Institute	1 affinity chromatography 2. ultrafiltration	No	Yes	No

TABLE II. FACTOR IX PRODUCTS LICENSED IN THE U.S (Continued)

B. COAGULATION FACTOR IX PRODUCTS DERIVED FROM HUMAN PLASMA

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Specific Activity of Final Product (IU/mg Protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
AlphaNine SD	Alpha	1 dual affinity chromatography 2 solvent detergent (TNBP and polysorbate 80) 3. nanofiltration (viral filter)	229 ± 23 (22)	Yes	Yes
Mononine	Aventis Behring	1. immunoaffinity chromatography 2 sodium thiocyanate 3 ultrafiltration	> 160	Yes (4)	No

TABLE II. FACTOR IX PRODUCTS LICENSED IN THE U.S (Continued)

C. PROTHROMBIN COMPLEX CONCENTRATES DERIVED FROM HUMAN PLASMA THAT CONTAIN FACTORS II, VII, IX, X (FOR USE IN PATIENTS WITH DEFICIENCIES OF FACTORS II, VII, X - NOTE THAT CONTENT VARIES FROM LOT TO LOT AND PRODUCT TO PRODUCT)

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity of Final Product (IU/mg Protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
Bebulin VH	Baxter Hyland Immuno (Vienna)	1. vapor heat (10h, 60°C, 1190 mbar pressure plus 1 h, 80°C, 1375 mbar)	2	Yes (6)	No
Konyne 80	Bayer	1 dry heat (80°C, 72 h)	1 25	No	Yes (5)
Profilnine SD	Alpha	1 solvent detergent (TNBP and polysorbate 80)	4 5	No	Yes
Proplex T	Baxter Hyland Immuno	1 dry heat (60°C, 144 h)	3 9	No	No

TABLE II. FACTOR IX PRODUCTS LICENSED IN THE U.S. (Continued)

D. ACTIVATED PROTHROMBIN COMPLEX CONCENTRATES DERIVED FROM HUMAN PLASMA (FOR USE IN PATIENTS WITH INHIBITORS TO FACTOR VIII OR IX)

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Specific Activity of Final Product (IU/mg Protein)	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
Autoplex T	Baxter Hyland Immuno (distributed by Nabi)	1. dry heat (60°C, 144h)	5	No	No
FEIBA VH	Baxter Hyland Immuno (Vienna)	1 vapor heat (10h, 60°C, 1190 mbar plus 1h, 80°C, 1375 mbar)	0 8	Yes (7)	Yes (7)

TABLE III. FACTOR VII PRODUCTS LICENSED IN THE UNITED STATES

A. RECOMBINANT FACTOR VIIa

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Contains Human Plasma Proteins?	Hepatitis Safety Studies in Humans with this Product	Hepatitis Safety Studies in Humans with Another Product, but Similar Viral Inactivation Method
NovoSeven	NovoNordisk (Bagsvaerd, Denmark)	1 affinity chromatography	No	Yes	No

TABLE IV. DESMOPRESSIN FORMULATIONS USEFUL IN DISORDERS OF HEMOSTASIS

Product Name	Manufacturer	U.S. Distributor	Formulation	Recommended Dosage and Administration
DDAVP (Injection)	Ferring AB (Malmo, Sweden)	Aventis Pharma	For parenteral (IV) or SQ use, 4 µg/ml in a 10 ml vial or 15 µg/ml in a 1 ml or 2 ml vial	1) 0.3 µg/kg, mixed in 30 ml normal saline solution, infused slowly over 30 minutes I.V. 2) 0.4 µg/kg subcutaneously Maximum dose 24 µg once every 24 hours May repeat after 24 hours.
Stimate (Nasal spray for bleeding)	Ferring AB (Malmo, Sweden)	Aventis Behring	Nasal spray, 1.5 mg/ml The metered dose pump delivers 0.1 ml (150 µg) per actuation The bottle contains 2.5 ml with spray pump capable of delivering 25 150-µg doses or 12 300-µg doses	In patients weighing <50 kg, one spray in one nostril delivers 150 µg For those weighing >50 kg, give one spray in each nostril (total dose 300 µg) May repeat after 24 hours

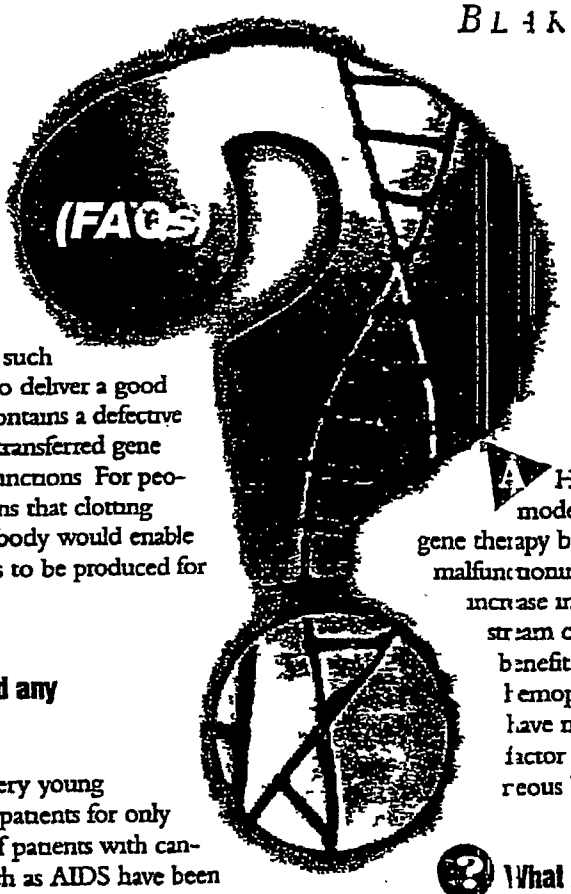
NATIONAL HEMOPHILIA FOUNDATION

NHF's Community Alert '99

VOL 6 NO 7 DECEMBER 1999

Frequently Asked Questions About Gene Therapy

BLAKE A ZEFF



See pages 6–9 for the 51st Annual Meeting photo spread

Q: What is gene therapy?

A: Gene therapy is an exciting experimental technique that seeks to provide the body with the genetic information (DNA) it lacks so that it can perform normal functions. Most gene therapy strategies use a vector, such as modified virus, to attempt to deliver a good copy of a gene to a cell that contains a defective gene. Scientists hope that the transferred gene will then restore the normal functions. For people with hemophilia, this means that clotting factor genes inserted into the body would enable normal clotting factor proteins to be produced for the first time.

Q: Has gene therapy cured any diseases so far?

A: No. Gene therapy is a very young science that has been used in patients for only about ten years. Thousands of patients with cancer and infectious diseases such as AIDS have been treated, but no one has been cured yet. While these are very difficult diseases to cure, scientists and physicians have shown that they can transfer genes into patients—an important first step. Some non-human animals have been cured of diseases using gene therapy, including dogs with hemophilia.

Q: Why is hemophilia well-suited for gene therapy?

A: Hemophilia is thought to be a model disease for treatment with gene therapy because it is caused by a single malfunctioning gene and only a small increase in clotting factor in the bloodstream could provide a great medical benefit. Making a patient with severe hemophilia (less than 1% factor level) have milder forms (greater than 5% factor level) should eliminate spontaneous bleeding episodes.

Q: What is currently being done in the field of gene therapy for hemophilia?

A: There are now three human trials underway—two for hemophilia A (factor VIII deficiency) and one for

Continued on Page 2 ▷

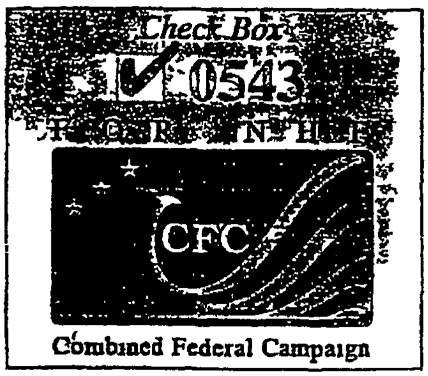
Gene Therapy

from page 1

hemophilia B (factor IX deficiency) The first gene therapy trial for hemophilia involves hemophilia A and a therapy developed by the Chiron Corporation, a California company In this small-scale phase 1 safety study, 20 patients will receive the gene for factor VIII through an injection into the veins of the arm. The gene is carried in a mouse retroviral vector, a virus that normally infects mice It has been modified to carry a short version of the factor VIII gene (B-domain deleted) and for use in humans Scientists expect that once inside the body the infused genetic material will be delivered to the liver and spleen eventually integrating into the cell's genetic material on a permanent level It does not cause disease in humans because its disease-causing genes have been removed from the retrovirus in order to insert the factor VIII gene

The other gene therapy trial for hemophilia A involves a form of therapy that takes place outside of the body A Massachusetts-based company, Transkaryotic Therapies, Inc, has developed a process beginning with patients undergoing skin biopsies to obtain connective tissue cells called fibroblasts A shortened version of the factor VIII gene (B-domain deleted) is then introduced into the fibroblasts by means of electroporation—a brief electrical pulse—and the cells are then grown to very large numbers in the laboratory Hundreds of millions of these new genetically corrected cells are then injected into the abdomen where they are expected to make factor VIII protein The cells are injected into the fat that surrounds the intestines, if enough of the protein gets into the systemic circulation, circulating clotting factor levels should increase

The final gene therapy trial underway for hemophilia involves a product named Coagulin-B—a treatment for hemophilia B Developed by California-based Avigen Inc and Katherine High, MD, from the University of Pennsylvania, the treatment uses a virus called an adeno-associated virus (AAV) injected into multiple sites in the thigh of the patient. Once taken up by muscle cells, it is believed they will make clotting proteins that will enter the bloodstream. Some dogs with factor IX deficiency treated with this viral vector have been cured for over two years This virus is used to deliver the gene because it is very good at infecting human cells It will not cause disease however, because much of its genetic material has been deleted to make room for the factor IX gene



Where are these trials being performed?

A The Chiron study is being conducted at the home bases of the following four researchers Dr Margaret Ragni, University of Pittsburgh, Dr Jerry Powell, University of California Davis, Dr Bruce Ewenstein, Harvard, Dr Gil White, University of North Carolina, Chapel Hill The Transkaryotic Therapies trial is being run with Dr David Roth, Harvard The Avigen study is being run by Dr Katherine High, University of Pennsylvania and Drs Mark Kay and Bert Glader, Stanford More sites may be added to these trials in the future if the Phase 1 results are encouraging

How successful have these trials been?

A Each of these trials [illegible] long time to get [illegible] many layers of [illegible] required to protect patients [illegible] As of press time [illegible] patients have been treated [illegible] the three trials

Phase 1 trials [illegible] small doses of an experimental drug and gradually [illegible] higher doses [illegible] the lower doses are [illegible] and [illegible] that would not necessarily be expected to produce measurable [illegible] clotting factors Reports from NHF's November 1999 Preconference Symposium on Gene Therapy [illegible] Meeting have suggested that some measurable effects are being seen in some patients although more patients need to be treated before any conclusions can be made [illegible]

Community Alert 99

NHF Community Alert [illegible]
National Hemophilia Foundation [illegible]
New York, NY [illegible]
[illegible]

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importantly, no medical problems have been found in any of the patients in any of the trials to date

When will we know the outcome from these clinical trials?

By next summer, these trials should be finished and much of the data will be analyzed It should be easy to determine if there have been positive results, clotting factor levels in the blood are being tested, the time it takes blood to clot is being measured, and numbers of bleeding episodes in patients are being monitored.

I heard recently that someone died as a result of gene therapy trials Are the people involved in the hemophilia trials at risk?

The trial where someone died is very different from the hemophilia trials The patient who died did not have hemophilia

Katherine High, MD, a physician and researcher involved in the hemophilia B gene therapy trials, notes that the hemophilia trials are not using the type of vector (adenovirus) used in the clinical trial that led to the fatality in the other case Further, Dr High points out that there has been no toxicity noted so far in any of the patients in the hemophilia B gene therapy trial with which she is involved Finally, Dr High emphasizes that the patient who died had a disease characterized by a deficiency of a liver enzyme required to remove toxic waste arising from protein breakdown It is a completely different disease from hemophilia

If gene therapy works for my son, does that mean the chance of someday passing his affected gene to a daughter is eliminated?

No, it doesn't The genetic information that a person has inherited from his parents would be passed down to his daughter Gene therapy to treat future generations or even unborn children with hemophilia is a hotly debated ethical issue that will be considered once trials such as these are successful

How long would gene therapy last?

No one can predict right now The goal is for it to last as long as possible, hopefully for years to come

What if these first three trials don't work?

Other scientific approaches, using improved viral vectors to carry the genes, are being developed in laboratories around the world Some of the most promising new techniques will be tested in persons with hemophilia in the next 1 to 2 years

What is the hope for gene therapy for hemophilia?

Scientists hope that one day gene therapy will provide the body with the genetic information needed to produce clotting factor on its own This would present significant improvement in the lives of persons with hemophilia In simple terms one can think of it as a treatment. But this treatment would last considerably longer than the 24 to 48 hours current clotting factor replacement therapy lasts That would make the gene therapy ' treatment" essentially a cure

What about gene therapy for other bleeding disorders?

Most attention has been focused on factor VIII and factor IX deficiency However, once positive results are seen in persons with these bleeding disorders, the stage will be set to develop therapies for other clotting factor deficiencies, including von Willebrand disease

What can I do?

It will be important for the bleeding disorders community to advocate and raise funds to more rapidly move gene therapy for hemophilia towards reality Getting more scientists to do research on hemophilia, both at medical schools and in the biotechnology industry will accelerate the cure Since no one can predict which method for delivering the genes is best, it helps for different scientific groups to use many different techniques The best ones will eventually get sorted out and pursued

Medical News

NHF Resolution on Hepatitis C

The NHF Board of Directors approved a resolution concerning hepatitis C on October 30, 1999 The resolution reads in part "A total population of people has been devastated by the outbreak of the deadly virus of hepatitis C It is imperative NHF look to both the present and future with a clearly defined goal of improving the treatment of those with HCV including an aggressive campaign of research, education oversight, and advocacy" To view the entire text of the resolution, please visit the NHF web site at www.hemophilia.org

Red Cross Launches Care 2000

The American Red Cross has increased support to the worldwide bleeding disorders community by recently launching CARE 2000, a multi-million dollar undertaking to fund clinical trials and research programs, as well as provide products to communities in need In addition to sponsoring medical conferences and college scholarships, CARE 2000 has supported NHF's *It's Time for a Cure* campaign with a pledge of $200,000, made last June

Continued on Page 10

January 2000 / Vol 2 / No 1

CDC's Universal Data Collection System

Report on the Universal Data Collection System (UDC)

Includes data collected from
May 1998 through October 1999

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *Report on the Universal Data Collection System* is published by the Hematologic Diseases Branch, Division of AIDS, STD and TB Laboratory Research, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia 30333 All data are provisional

Suggested Citation Centers for Disease Control and Prevention Report on the Universal Data Collection System 2000,2(No 1) [inclusive page numbers]

Single copies of the *Report on the Universal Data Collection System* are available free from HANDI, the information service of the National Hemophilia Foundation by calling (800) 42-HANDI Confidential information, referrals, and educational materials on hemophilia and other bleeding disorders is also available through HANDI The *Report on the Universal Data Collection System* is accessible via internet at http //www cdc gov nccdc dastlr/Hematology/HDBarchive htm

Contents

Commentary

The two most common congenital bleeding disorders are von Willebrand disease (vWD) and hemophilia. vWD is caused by defective synthesis or function of a protein, called von Willebrand factor, which is necessary for normal blood clotting. vWD occurs with equal frequency in men and women. Although the prevalence of this disease is not precisely known, it is estimated that between one and two percent of the population are affected. There are different types and severity of vWD. Symptoms include heavy or prolonged menstrual bleeding, easy bruising, frequent or prolonged nosebleeds, and prolonged bleeding following surgery, dental work, childbirth, or injury.

Hemophilia is caused by a defect in the gene located on the X chromosome that contains the genetic code for one of the clotting factor proteins necessary for normal blood clotting. A deficiency of factor VIII is referred to as hemophilia A or "classic" hemophilia. In contrast, a deficiency of factor IX characterizes hemophilia B, also known as Christmas disease. The defect usually occurs on one of the two female X chromosomes and results in a carrier state. When males have the defect on their only X chromosome, they are affected with the disease. Thus, almost all of the approximately 17,000 persons with hemophilia in the United States are male.

People with severe hemophilia can experience serious bleeding into tissues, muscles, joints, and internal organs, often without any obvious trauma. Repeated bleeding into joints without adequate treatment results in crippling chronic joint disease, one of the severe complications of bleeding disorders. In the mid-1970s, treatment for hemophilia was improved through the use of clotting factor concentrates, products made from the plasma of donated blood. However, because blood donations from thousands of donors are pooled together to make these products, many persons with bleeding disorders were infected with hepatitis B and C viruses and with human immunodeficiency virus (HIV), the virus that causes AIDS, before the risk of disease transmission in blood products was recognized and prevention measures taken.

In 1975, Congress initiated federal funding to specialized hemophilia treatment centers (HTCs) to provide comprehensive care to persons with bleeding disorders. Since 1986, CDC has been involved with the hemophilia community through the HTC system, primarily through risk-reduction efforts aimed at preventing secondary infection of family members with HIV.

In 1991, CDC received a request from the National Hemophilia Foundation to expand their collaborative activities with the bleeding disorders community. Meetings with patients and hemophilia care providers were held during 1992 to determine the areas of highest priority. Based on recommendations from these constituents, a Congressional mandate was issued to CDC with the goal of reducing the human suffering and financial burden of bleeding disorders by focusing national emphasis on prevention and early intervention. The issues of greatest concern identified by the bleeding disorders community were 1) the safety of the blood supply from infectious diseases, and 2) the prevention of joint disease.

In response, CDC developed the Universal Data Collection System (UDC). The purpose of UDC is two-fold: 1) to establish a sensitive blood safety monitoring system among persons with bleeding disorders and 2) to collect a uniform set of clinical outcomes information that could be used to monitor the occurrence of and potential risk factors for infectious diseases and joint complications.

Persons with bleeding disorders are enrolled in UDC by care providers in each of the nation's 134 federally funded HTCs. As part of the project, a uniform set of clinical data and a plasma specimens are collected by HTC

staff each year during the participant's annual comprehensive clinic visit A portion of the plasma specimen is used to perform free screening tests for hepatitis A, B, and C viruses and for HIV The remainder of the specimen is stored for use as needed in future blood safety investigations

Enrollment in UDC began in May 1998 Information about eligibility requirements, enrollment procedures, and data collection can be found in the *Technical Notes* of this report Participating HTCs are listed by region in the *Acknowledgements* A regional map is included at the end of this report

The purpose of this surveillance report is to disseminate the information being collected by this project to public health workers, health educators and planners, other care providers, and patients in the bleeding disorders community The report contains information about the demographic characteristics of the participants, their blood and factor product use, and the occurrence and treatment of joint and infectious diseases We hope that this information will prove useful to those involved in efforts to reduce or prevent the complications of these conditions

The proper interpretation and appropriate use of surveillance data require an understanding of how the data are collected, reported, and analyzed Therefore, readers of this report are encouraged to review the *Technical Notes*, beginning on page 18

Suggested Reading

CDC Prevention of hepatitis A through active or passive immunization Recommendations of the Advisory Committee on Immunization Practices (ACIP) *MMWR* 1996,45(No RR-15) 1-30

CDC Transmission of hepatitis C virus infection associated with home infusion therapy for hemophilia *MMWR* 1997,46 597-599

CDC Occurrence of hemophilia in the United States American Journal of Hematology 1998, 59 288-294

Hill H, Stein S Viral infections among patients with hemophilia in the state of Georgia American Journal of Hematology 1998,59 36-41

The following publications are available from HANDI (800-42?-HANDI)

- *What You Should Know about Bleeding Disorders* (1997)

- *Comprehensive Care for People with Hemophilia* by Shelby Dietrich, MD (1991)

- *Understanding Hepatitis* by Leonard Seeff, MD (1997)

- *HIV Disease in People with Hemophilia. Your Questions Answered* by Glenn Pierce, MD, PhD (1991)

- *Bleeding Disorders and AIDS The Facts* (1997)

- Information packet on von Willebrand disease

Table 1. Enrollment in UDC, May 1998 – October 1999

Month	Number Enrolled	Number Refused	Refusal Rate (%)
May – Oct, 1998	988	85	7 9
November	224	25	10 3
December	219	26	10 6
January, 1999	318	25	7 3
February	359	38	9 6
March	368	49	11 8
April	363	40	9 9
May	359	43	10 7
June	415	40	8 8
July	307	42	12 0
August	355	64	15 3
September	297	54	15 4
October	236	43	15 4
Total	**4808**	**574**	**10 7**

Table 2. Regional* enrollment activity, May 1998 – October 1999

Region	Number Approached	Refusal rate (%)
I	216	11 6
II	776	12 6
III	805	16 4
IV-N	480	6 3
IV-S	308	10 7
V-E	289	11 8
V-W	633	7 6
VI	628	13 1
VII	206	11 7
VIII	327	3 7
IX	634	7 9
X	14	0

*See map (page 24) for regional designations

Table 3. Demographic characteristics of persons* enrolled in UDC

Characteristic	Hemophilia A (n = 3248) Number	Hemophilia A (n = 3248) Percent	Hemophilia B (n = 761) Number	Hemophilia B (n = 761) Percent	vWD (n = 723) Number	vWD (n = 723) Percent
Age Group (years)						
2 – 10	918	28 4	192	25 3	199	27 6
11 – 20	1007	31 1	199	26 3	262	36 3
21 – 40	798	24 6	229	30 2	131	18 1
41 – 60	443	13 7	108	14 2	93	12 9
61+	72	2 2	30	4 0	37	5 1
Race / Ethnicity						
White	2236	68 9	556	73 1	529	73 2
African American	391	12 0	92	12 1	28	3 9
Hispanic	416	12 8	81	10 6	69	9 5
Asian / Pacific Islander	78	2 4	8	1 1	21	2 9
Native American	27	0 8	6	0 8	7	1 0
Other	99	3 0	18	2 4	69	9 5
Sex						
Male	3189	98 2	743	97 6	342	47 3
Female	59	1 8	18	2 4	381	52 7

*Twenty-four persons were reported to have both hemophilia and vWD, and 98 persons had a bleeding disorder other than hemophilia or vWD

Table 4. Disease severity of persons enrolled in UDC

	Hemophilia Mild N	Hemophilia Mild %	Hemophilia Moderate N	Hemophilia Moderate %	Hemophilia Severe N	Hemophilia Severe %	vWD Type 1 & 2 N	vWD Type 1 & 2 %	vWD Type 3 N	vWD Type 3 %
Participants*	821	20 5	919	23 0	2261	56 5	580	88 5	75	11 5

*Numbers do not equal total number of persons because of missing data

Table 5. Bleeding episodes* among persons enrolled in UDC by disease severity and prophylaxis status

No prophylaxis

	Hemophilia			vWD	
Bleeding site	Mild n = 817	Moderate n = 825	Severe n = 1687	Type 1 & 2 n = 560	Type 3 n = 74
Joint	0 6 (2 3)	3 8 (7 8)	9 3 (12 1)	0 2 (1 6)	3 7 (8 3
Muscle	0 3 (1 0)	1 1 (2 4)	2 6 (5 8)	0 1 (0 8)	0 5 (1 3
Other	0 7 (2.9)	1 4 (4 4)	2 0 (4 7)	3 1 (8 4)	3 9 (6 5
All sites					
Mean	1 7 (4 1)	6 2 (10 3)	13 9 (16 1)	3 4 (8 6)	8 C (1C 5
Median	0	3	10	0	4

With prophylaxis

	Hemophilia		
Bleeding site	Mild N = 3	Moderate n = 49	Severe n = 315
Joint	0 5 (1 0)	2 7 (4 0)	3 2 (5 8)
Muscle	0 (—)	1 1 (5 4)	0 8 (2 2)
Other	1 2 (1 5)	1 2 (3 3)	1 4 (6 4)
All sites			
Mean	1 8 (1 3)	5 1 (9 3)	5 4 (9 5)
Median	2	3	2

*Values are mean (±SD) number of bleeding episodes experienced during the 6-month period preceding the UDC visit

Table 6. Blood and factor products used* by persons enrolled in UDC

Treatment product	Hemophilia A		Hemophilia B		vWD	
	Number	Percent	Number	Percent	Number	Percent
Recombinant factor	1991	61 3	406	53 4	4	0 6
Monoclonal factor VIII	664	20 4	1	0 1	2	0 3
Other human factor	156	4 8	1	0 1	148	21 2
Porcine factor VIII	6	0 2	0	—	0	—
Purified factor IX	2	0 1	277	36 4	0	—
Prothrombin complex	59	1 8	32	4 2	0	—
Activated prothrombin complex	156	4 8	11	1 4	0	—
Cryoprecipitate or FFP	12	0 4	5	0 7	14	2 0
Desmopressin	191	5 9	2	0 3	263	37 6
None used	294	9 1	122	16 0	259	37 1

*Any use of the product(s) during the 12-month period preceding UDC enrollment

NOTE Individuals may have used more than one type of treatment product

Table 7. Infectious disease complications among persons enrolled in UDC

	Hemophilia		vWD	
Infectious Disease Complications	Number	% of Total	Number	% of Total
Risk factors for liver disease				
Past/present hepatitis B virus infection	808	20 2	25	3 5
Past/present hepatitis C virus infection	1883	47 0	59	8 2
History of alcohol abuse	147	3 7	3	0 4
Other	41	1 0	8	1 1
None	2033	50 7	650	89 9
Signs or symptoms of liver disease (During the last year)				
Jaundice	27	0 7	1	0 1
Ascites	25	0 6	1	0 1
Varices	17	0 4	0	—
Other	45	1 1	1	0 1
None	3920	97 8	720	99 6
Laboratory markers of liver disease				
Chronically elevated ALT/AST levels	721	18 0	15	2 1
Elevated prothrombin time in the last year	101	2 5	10	1 4
Therapy for chronic viral hepatitis				
Any therapy	167	4 2	5	0 7
Successful therapy	30	18 0*	1	20 0*
Intravenous access devices (IVAD)				
Used an IVAD in the last year	496	12 4	24	3 3
IVAD infection in the last year	66	13 3**	3	12 5**

*Percent of persons who received any therapy for chronic viral hepatitis

**Percent of persons who used an IVAD in the last year

Figure 1. **Prevalence of hepatitis A virus exposure and reported vaccination status among persons with hemophilia**

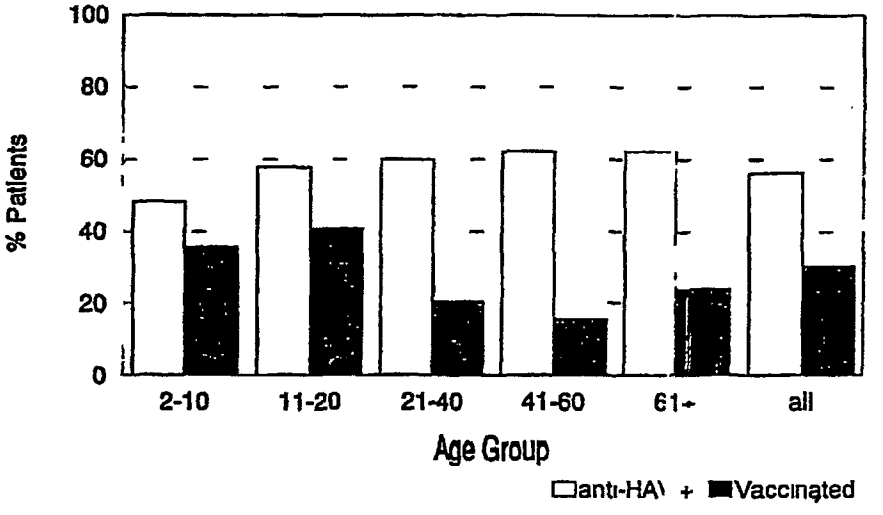
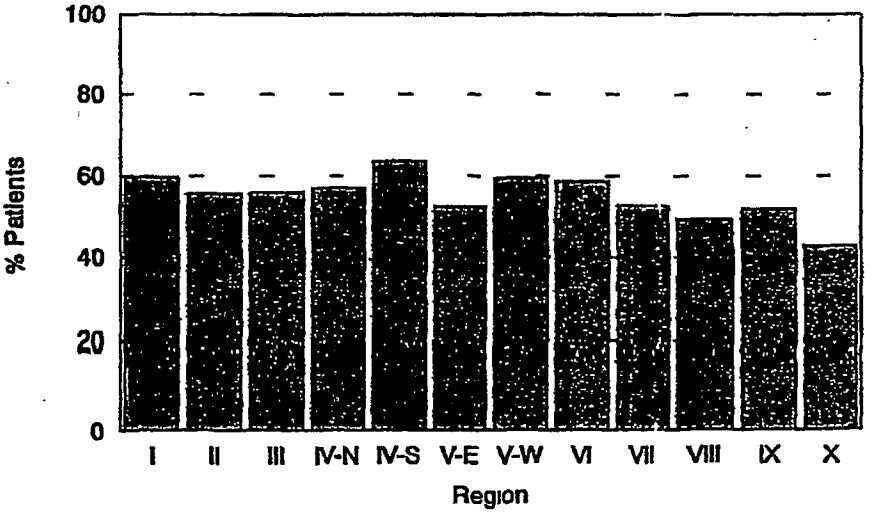


Figure 2. **Regional* distribution of natural and acquired immunity to hepatitis A virus among persons with hemophilia**



*See map (page 24) for regional designations

Figure 3. **Prevalence of hepatitis A virus exposure and reported vaccination status among persons with vWD**

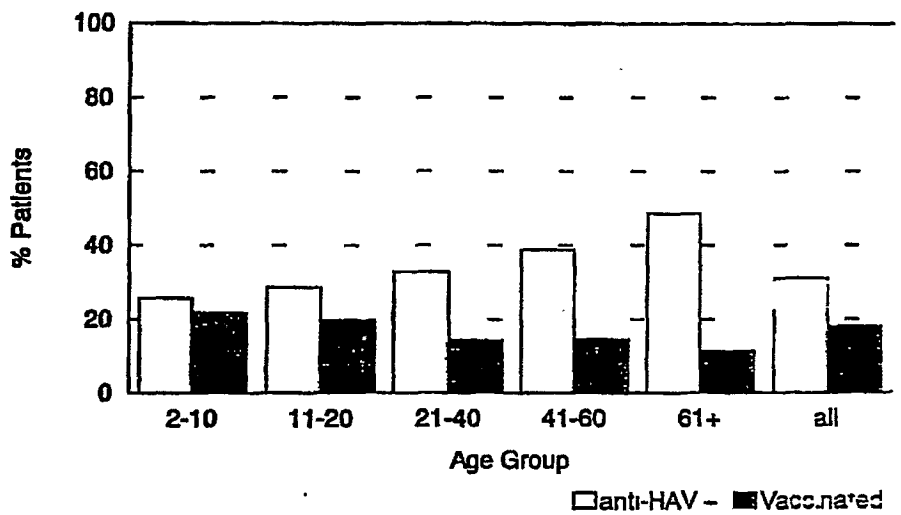


Figure 4. **Prevalence of hepatitis B virus exposure and reported vaccination status among persons with hemophilia**

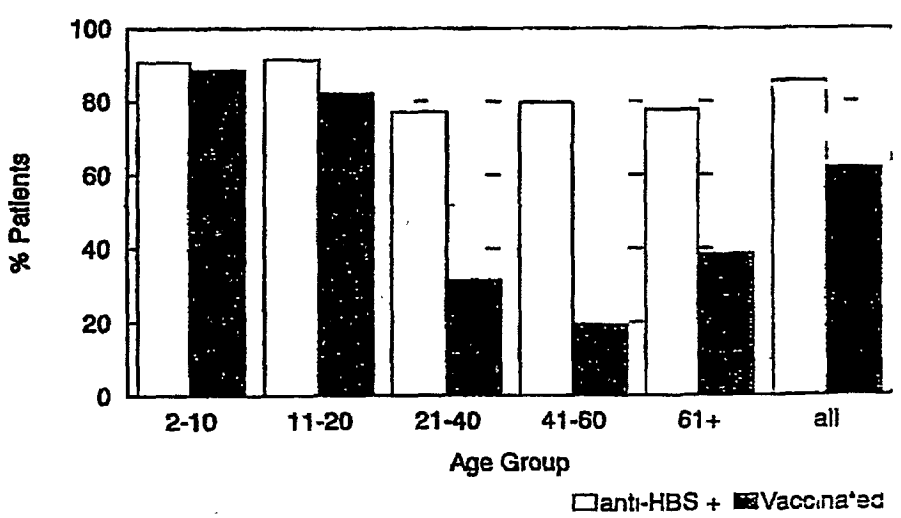
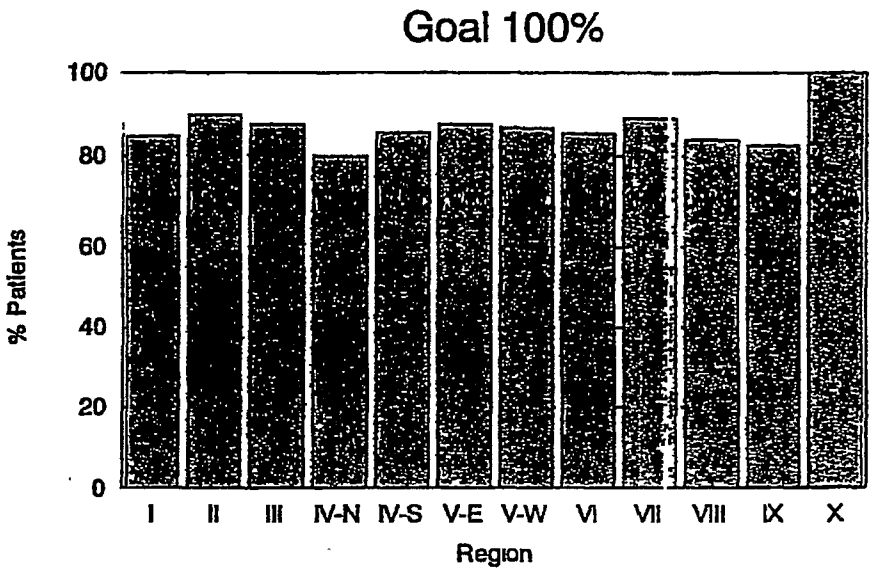


Figure 5 **Regional* distribution of natural and acquired immunity to hepatitis B virus among persons with hemophilia**



*See map (page 24) for regional designations

Figure 6 **Prevalence of hepatitis B virus exposure and reported vaccination status among persons with vWD**

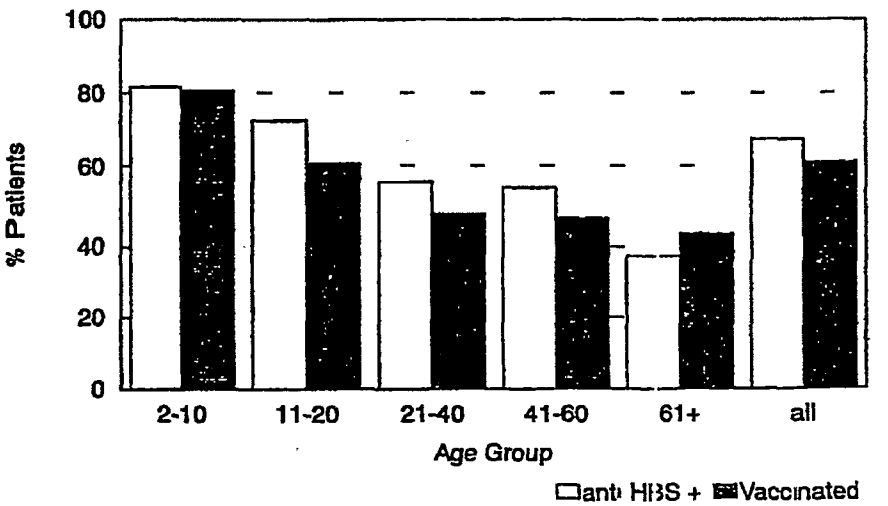


Figure 7. **Prevalence of hepatitis C virus infection among persons with bleeding disorders**

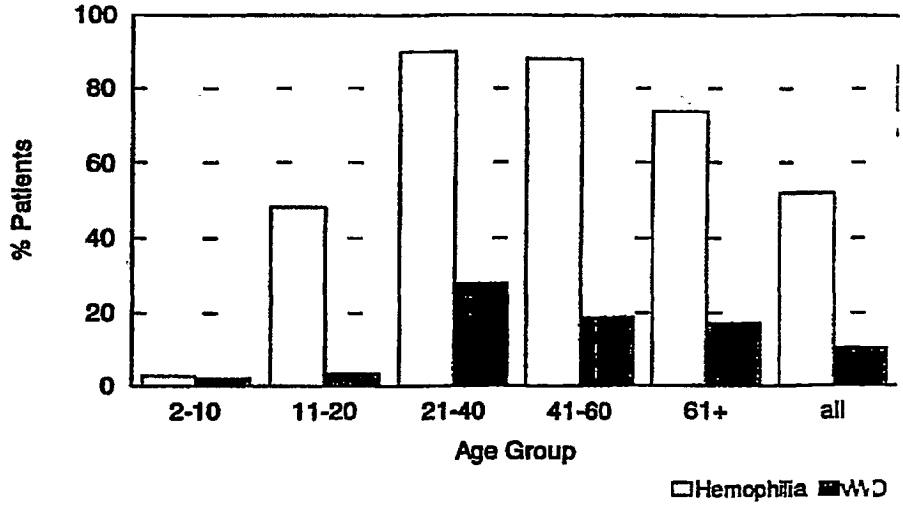


Figure 8. **Prevalence of human immunodeficiency virus (HIV) infection among persons with bleeding disorders**

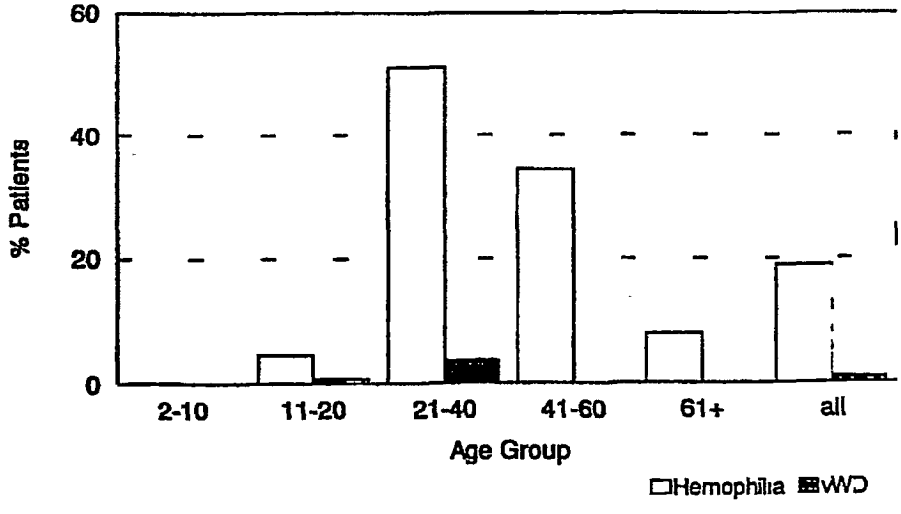


Table 8. Treatment type for persons with hemophilia enrolled in UDC

Severity	Total number	Episodic care No (%)	Number on intermittent prophylaxis	Number on continuous* prophylaxis
Mild	821	808 (98 4)	9	4
Moderate	919	784 (85 3)	41	94
Severe	2261	1503 (66 5)	186	572

*Prophylaxis is considered continuous when administered for at least 46 weeks per year

Table 9. Prevalence of current inhibitors by titer* among persons with hemophilia enrolled in UDC

	Hemophilia A			Hemophilia B		
Severity	Number	Low titer	High titer	Number	Low titer	High titer
Mild	650	2 (0 1)	1 (0 03)	171	0	0
Moderate	659	11 (1 7)	9 (1 4)	260	0	1 (0 4)
Severe	1932	74 (3 8)	116 (6 0)	329	4 (1 2)	15 (4 6)

*Low titer is defined as an inhibitor level of 0 5 – 5 Bethesda units (BU)
High titer is defined as an inhibitor level of >5 BU
Numbers in parentheses are percents

Table 10. Intra-cranial hemorrhage (ICH)* among persons with hemophilia enrolled in UDC

	Hemophilia A		Hemophilia B	
Severity	Total	No with ICH (%)	Total	No with ICH (%)
Mild	650	1 (0 2)	171	0
Moderate	659	6 (0 9)	260	1 (0 4)
Severe	1932	21 (1 1)	329	4 (1 2)

Causes of ICH	Number (%)
Trauma	15 (53 6)
Thrombocytopenia	1 (3 6)
Other	12 (42 9)

*Diagnosed by a physician during the year prior to the UDC visit

Table 11 Joint complications among persons enrolled in UDC

	Hemophilia						vWD			
	Mild		Moderate		Severe		Type 1 & 2		Type 3	
	N	%	N	%	N	%	N	%	N	%
Target joint*	73	8 9	281	30 6	1129	49 9	10	1 8	17	22 7
Invasive procedure	33	4 0	63	6 9	277	12 2	9	1 6	7	9 3
Joint infection	6	0 7	14	1 5	39	1 7	3	0 5	0	—
Used cane	114	13 9	230	25 0	711	31 4	35	6 2	16	21 3
Used wheelchair	14	1 7	60	6 5	236	10 4	15	2 7	4	5 3
Any activity restriction	119	14 5	282	30 7	957	42 3	40	7 1	21	28 0

*Please see Technical Notes (page 18) for the definition of a target joint

Table 12. Joint limitations among persons enrolled in UDC

	Hemophilia			vWD	
	Mild	Moderate	Severe	Type 1 & 2	Type 3
Number of patients	777	841	1992	531	70
Mean indicator* value	53 7	96 9	159 4	28 2	67 0
Standard deviation	99 4	175 7	220 8	67 0	110 3

*Indicator is the total number of degrees of range of motion less than normal for five joints The joint motions measured and normal values used (in parentheses) are hip extension (30), hip flexion (120), knee flexion (135), knee extension (0), shoulder flexion (180), elbow flexion (150), elbow extension (0), elbow pronation and supination (80), ankle dorsiflexion (20), ankle plantar flexion (50) Any hyperextension of the knee or elbow is not included in the calculation In UDC, limitations in knee and elbow extension are recorded as negative numbers Patients with missing measures for any of the joints are excluded from the analyses As an example, patients with mild hemophilia have on average 53 7 degrees less than normal range of motion across ten joints

Technical Notes

Eligibility Requirements

To participate in UDC, patients must receive care in a federally funded HTC and meet at least one of the following criteria 1) age 2 years or older with a bleeding disorder due to congenital deficiency or acquired inhibitors in which any of the coagulation proteins is missing, reduced, or defective and has a functional level of less than 50 percent, or 2) age 2 years or older with a diagnosis by a physician of von Willebrand disease Individuals specifically excluded from participation in UDC include persons with any of the following 1) an exclusive diagnosis of a platelet disorder, 2) thrombophilia; or 3) coagulation protein deficiencies due to liver failure

Data collection

UDC data are collected during the participant's "annual visit," which ideally should occur once each calendar year (January-December), with the interval between visits as close as possible to 12 months Data are collected according to guidelines and definitions detailed in surveillance manuals provided to HTC staff by CDC Informed consent for participation is obtained each year Demographic information and reasons for refusal are obtained using a Patient Refusal Form for all eligible persons who decline participation To protect patient confidentiality, all data sent to CDC do not contain personally identifying information, but rather use a unique 12-digit code that is generated by a computer software program supplied to HTCs by CDC

Eligible participants are registered into UDC through a Registration Form completed by HTC staff, this form includes patient demographic, diagnostic, and historical information Month and year of birth are used to calculate age on the last day of the current year Information on race and ethnicity is obtained from clinic records and may have been based either on self-report or on observations made by care providers

During the annual visit clinical information is recorded on a standardized data collection form (Annual Visit Form) In addition to information about education, employment status and health insurance, data are also collected about treatment type (episodic vs prophylactic), presence and treatment of inhibitors the number of bleeding episodes experienced (based on infusion logs or patient recall) type and brand name of all factor concentrates or other treatment products used and whether or not clotting factor is infused at home

Information regarding infectious diseases is also collected including risk factors and clinical signs, symptoms and laboratory markers of liver disease Data are also recorded about any therapy for chronic hepatitis, the status of vaccination for hepatitis A and B viruses, and, among patients with an intravenous access device, the occurrence of a device-associated infection Persons ≥ 18 years of age who are HIV-infected are asked several questions concerning risk-reduction activities including partner testing and condom use

Data are also collected on joint disease, including the use of walking aids the occurrence of joint infections, and measures of impact of joint disease on daily activities During the visit, range of motion measurements on five joints (hip, knee, shoulder, elbow, and ankle) are taken by a physical therapist or other trained health care provider according to detailed guidelines provided in a reference manual supplied by CDC All health care providers performing these measurements are trained and certified by regional physical therapists who have themselves received centralized training In addition information about whether a particular joint is a "target joint" or whether the participant has

required the use of an orthopedic appliance or has undergone an invasive orthopedic procedure is collected In UDC, a target joint is defined as a joint in which recurrent bleeding has occurred on four or more occasions during the previous 6 months or one in which 20 life-time bleeding episodes have occurred

All data collection forms are sent overnight to CDC where they are then key entered into a computer database using double-entry software to minimize data entry errors Data are then screened for omissions, inconsistencies, and unusual values that possibly represent abstraction or data-entry errors Error reports are generated and faxed to the HTC, where a designated UDC contact uses available information to resolve discrepancies and complete missing data items

Laboratory testing

During the annual visit, a blood specimen is obtained from each participant in UDC The specimen is processed by HTC personnel according to guidelines provided by CDC that are designed to minimize the effects of storage and shipment on subsequent analyses Samples are shipped overnight to the CDC Serum Bank where they are aliquoted and stored A portion of the specimen is sent to the Eugene B Casey Hepatitis Laboratory at Baylor College of Medicine in Houston, Texas A second portion is sent to the HIV Testing Laboratory at CDC The remainder of the specimen is stored in the CDC Serum Bank for future blood safety investigations, as needed

Testing for hepatitis A, B, and C viruses follow algorithms designed to determine with the highest probability the patient's status with regard to exposure to or infection with these viruses Information provided by HTC staff on a Laboratory Form, including the results of previous local testing and vaccination history, is used by personnel at the testing laboratory to provide a detailed interpretation of the test results

Testing for HIV follows algorithms designed to determine patient status with regard to infection with HIV-1 and HIV-2 The results of all laboratory testing are reported to the HTC using the CDC unique code which can be matched to the patient only by HTC staff

Mortality reporting

Deaths occurring among all HTC patients (regardless of whether or not they have been enrolled in UDC) are reported to CDC using a Mortality Form Data collected include age at death, sex, race/ethnicity, disease type and severity, and whether or not blood products had been used during the year prior to death Additionally, information about the death, including the date, cause (primary and contributing), and whether or not an autopsy was performed, is also collected

Tabulation and presentation of data

Data in this report are provisional The data presented in this report represent the first 18 months of what is planned to be at least a 5-year surveillance project Future reports will include expanded data tables to cover subsequent surveillance periods and will provide the results of more detailed analyses of available data and findings from special studies

Acknowledgements

We thank the Regional Coordinators (listed below in italics) of the federal HTC regions for their assistance in the implementation and technical support of UDC. Data for this report were collected by care providers in HTCs at the following institutions:

Region I
Ann Forsberg, MA, MPH
New England Hemophilia Center
Worcester, MA
Dartmouth-Hitchcock Hemophilia Center
Lebanon, NH
Rhode Island Hospital
Providence, RI
UCONN Hemophilia Treatment Center
Farmington, CT
Vermont Regional Hemophilia Center
Burlington, VT
Boston Children's Hospital
Boston, MA

Region II
Mariam Voutsis, RN, MPA
The New York Hospital
New York, NY
Puerto Rico Hemophilia Treatment Center
San Juan, PR
UMDNJ-Robert Wood Johnson University
Hospital, New Brunswick, NJ
Nadeene Brunini Comprehensive
Hemophilia Care Center, Newark, NJ
The Mary M. Gooley Hemophilia Center, Inc.
Rochester, NY
SUNY Health Science Center - Adult
Syracuse, NY
SUNY Health Science Center - Pediatric
Syracuse, NY
Hemophilia Center of Western New York –
Adult, Buffalo, NY
Hemophilia Center of Western New York –
Pediatric, Buffalo, NY
Albany Medical College
Albany, NY
UHSH Blood Disorders Center
Johnson City, NY
Mount Sinai Medical Center
New York, NY
Long Island Jewish Medical Center
New Hyde Park, NY

Region III
Sue Cutter, MSW, MPA
Children's National Medical Center
Washington, DC
Georgetown University Medical Center
Washington, DC
University of Virginia Hospital
Charlottesville, VA
Medical College of Virginia Hospital
Richmond, VA
Children's Hospital of the King's Daughters
Norfolk, VA
Cardeza Foundation Hemophilia Center
Philadelphia, PA
Christiana Care Health Services
Newark, DE
Hemophilia Center of Central Pennsylvania
Hershey, PA
Hemophilia Center of Western Pennsylvania
Pittsburgh, PA
West Virginia University Medical Center
Morgantown, WV
Charleston Area Medical Center
Charleston, WV
Johns Hopkins University Medical Center
Baltimore, MD
Children's Hospital of Philadelphia Specialty
Center, Voorhees, NJ
Children's Hospital of Philadelphia
Philadelphia, PA
Lehigh Valley Hospital
Allentown, PA

Region IV-N
Richard J Atwood, M.A., M P H
Wake Forest University School of Medicine
Winston-Salem, NC
Brown Cancer Center
Louisville, KY
Children's Hospital of Palmetto –
Richland Memorial, Columbia, SC
University of Tennessee – Memphis
Memphis, TN
East Tennessee Comprehensive Hemophilia
Center, Knoxville, TN
Vanderbilt University Medical Center
Nashville, TN
University of North Carolina at Chapel Hill
Chapel Hill, NC
Norton Kosair Children's Medical Center
Louisville, KY

Region IV-S
Crystal D Watson, B S W
Miami Comprehensive Hemophilia Center –
Pediatrics, Miami, FL
University of Florida
Gainesville, FL
Scottish Rite Children's Medical Center
Atlanta, GA
Medical College of Georgia - Adult
Augusta, GA
University of Mississippi Medical Center
Jackson, MS
Miami Comprehensive Hemophilia Center –
Adult, Miami, FL
Children's Rehabilitation Services
Mobile, AL
Children's Rehabilitation Services
Birmingham, AL
Children's Rehabilitation Services
Opelika, AL
Children's Rehabilitation Services
Huntsville, AL
Emory University Hemophilia Program
Office
Atlanta, GA
University of South Florida – Pediatric
Tampa, FL

Region V-E
Tamara Wood-Lively, M H A , J D
Munson Medical Center
Traverse City, MI
Hemophilia Clinic of West Michigan Cancer
Center, Kalamazoo, MI
University of Cincinnati Medical Center
Cincinnati, OH
The Children's Medical Center
Dayton, OH
Michigan State University Comprehensive
Center for Bleeding Disorders
East Lansing MI
Children's Hospital of Michigan
Detroit, MI
DeVos Children's Hospital at Butterworth
Grand Rapids, MI
Eastern Michigan Hemophilia Treatment
Center, Flint, MI
Ohio State University Medical Center
Columbus, OH

Region V-W
Mary Anne Schall, R N , M S
Northwestern University
Chicago, IL
Cook County Hospital - Adult
Chicago, IL
Children's Memorial Hospital
Chicago, IL
Comprehensive Bleeding Disorders Center
Peoria, IL
Fairview - University Medical Center
Minneapolis MN
Mayo Clinic
Rochester, MN
MeritCare Hospital DBA Roger Maris
Cancer Center, Fargo, ND
Hemophilia Outreach Centre
Green Bay, WI
Gunderson Clinic
LaCrosse, WI
American Red Cross - Badger Chapter
Madison, WI
Rush Children's Hospital
Chicago, IL
Michael Reese Hospital – Adult

Chicago, IL
South Dakota Children's Specialty Clinics
Sioux Falls, SD
Comprehensive Center for Bleeding
Disorders, Milwaukee, WI
Cook County Children's Hospital
Chicago, IL

Region VI
John Drake, R N , M S N
Gulf States Hemophilia and Thrombosis
Center, Houston, TX
Louisiana Comprehensive Hemophilia
Center, New Orleans, LA
Arkansas Children's Hospital
Little Rock, AR
Oklahoma Comprehensive Hemophilia
Treatment Center, Oklahoma City, OK
Cook Children's Medical Center
Ft Worth, TX
South Texas Comprehensive Hemophilia
Center, San Antonio, TX
Children's Medical Center
Dallas, TX
University of Texas Southwestern Medical
School, Dallas, TX

Region VII
Mike Lammer, MSW
University of Iowa Hospitals and Clinics
Iowa City, IA
Cardinal Glennon Children's Hospital
St Louis, MO
Kansas City Regional Hemophilia Center
Kansas City, MO
Nebraska Regional Hemophilia Treatment
Center, Omaha, NE
St Louis University Medical Center
St Louis, MO
University of Missouri Hospital and Clinics
Columbia, MO

Region VIII
Mary Lou Damiano, R N , M Ed
Mountain States Regional Hemophilia and
Thrombosis Center, Denver, CO
Ted R Montoya Hemophilia Center
Albuquerque, NM
Mountain States Regional Hemophilia Center
Tucson, AZ
Phoenix Children's Hospital
Phoenix, AZ
Mountain States Regional Hemophilia Center
– Utah, Salt Lake City, UT

Region IX
Judith Baker, M H S A
Children's Hospital of Los Angeles
Los Angeles, CA
Alta Bates Medical Center
Berkeley, CA
University of California at Davis
Sacramento, CA
University of California, San Francisco
San Francisco, CA
Orthopaedic Hospital of Los Angeles
Los Angeles, CA
Children's Hospital, San Diego
San Diego, CA
Children's Hospital of Orange County
Orange, CA
Children's Hospital Oakland
Oakland, CA
Hemophilia and Thrombosis Center of
Nevada, Las Vegas, NV
Guam Comprehensive Hemophilia Care
Program, Agana, GU
City of Hope National Medical Center
Duarte, CA
Lucile Salter Packard Children's Hospital
at Stanford, Palo Alto, CA
University of California
San Diego, CA

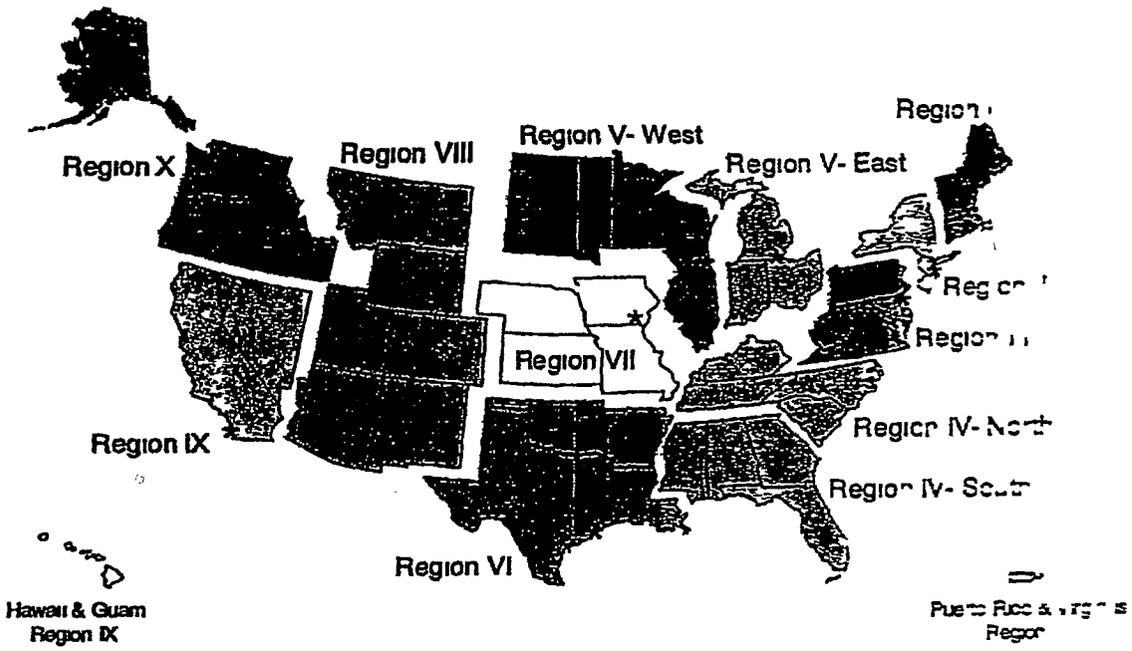
Region X

Robina Ingram-Rich, R N , M S , M P H
Puget Sound Blood Center and Program
Seattle, WA
Oregon Hemophilia Treatment Center
Portland, OR

We would also like to acknowledge the assistance of the UDC Working Group, which is composed of the following individuals

Randall Curtis, M B A
Berkeley, CA
Bruce M Ewenstein, M D
Boston, MA
Ann Forsberg, M A , M P H
Worcester, MA
Sue Geraghty, R N , M B A
Aurora, CO
W Keith Hoots, M D
Houston, TX
Heather Huszti, Ph D
Oklahoma City, OK
Marion Koerper, M D
San Francisco, CA
Jeanne Lusher, M D
Detroit, MI
Peter Smith, M D
Providence, RI
Scott Ward, RPT, Ph D
Salt Lake City, UT
Gilbert C, White, II, M D
Chapel Hill, NC

Hemophilia Treatment Center Regions



*Denotes location of regional core centers

TABLE V. FRESH FROZEN PLASMA

Product Name	Manufacturer	Method of Viral Depletion or Inactivation	Pool Size, Units
Donor Retested Fresh Frozen Plasma	Community blood banks (not ARC)	1. Donors must test negative on second donation in order for first donation to be released	1
Plas + SD	Vitex from plasma collected by ARC (distributed by ARC)	1 Solvent detergent (TNBP and polysorbate 80)	2500

ReFVIII Conjoint Study Report

Baxter

Interoffice Memorandum—For Internal Use Only

To Distribution

Date June 28, 2000

From Jelena Popadic

Distribution M Baldridge, A Baumann, T Comiskey, B Connolly*, H Ehrlich, E Gomberts, L Gunheen, C Immel, H Halbritter, J Hauert, D Hernandez, M Inoue J Reuter S Reindl*, N Riedel, D Swan, G Thomas, I Thomas, J Weinstein* (Included Appendix I with report*

Re Recombinant FVIII Conjoint Study Report

Please find your copy of the Recombinant FVIII report that was prepared to summarize the results of the conjoint study The study was a global/US initiative commissioned by Teresa Comiskey and Jim Hauert This custom study took place in eight countries and involved 333 respondents The participants in the research were asked to trade off several product features as described in the report A summary of the results can be found in the ***Management Summary*** section

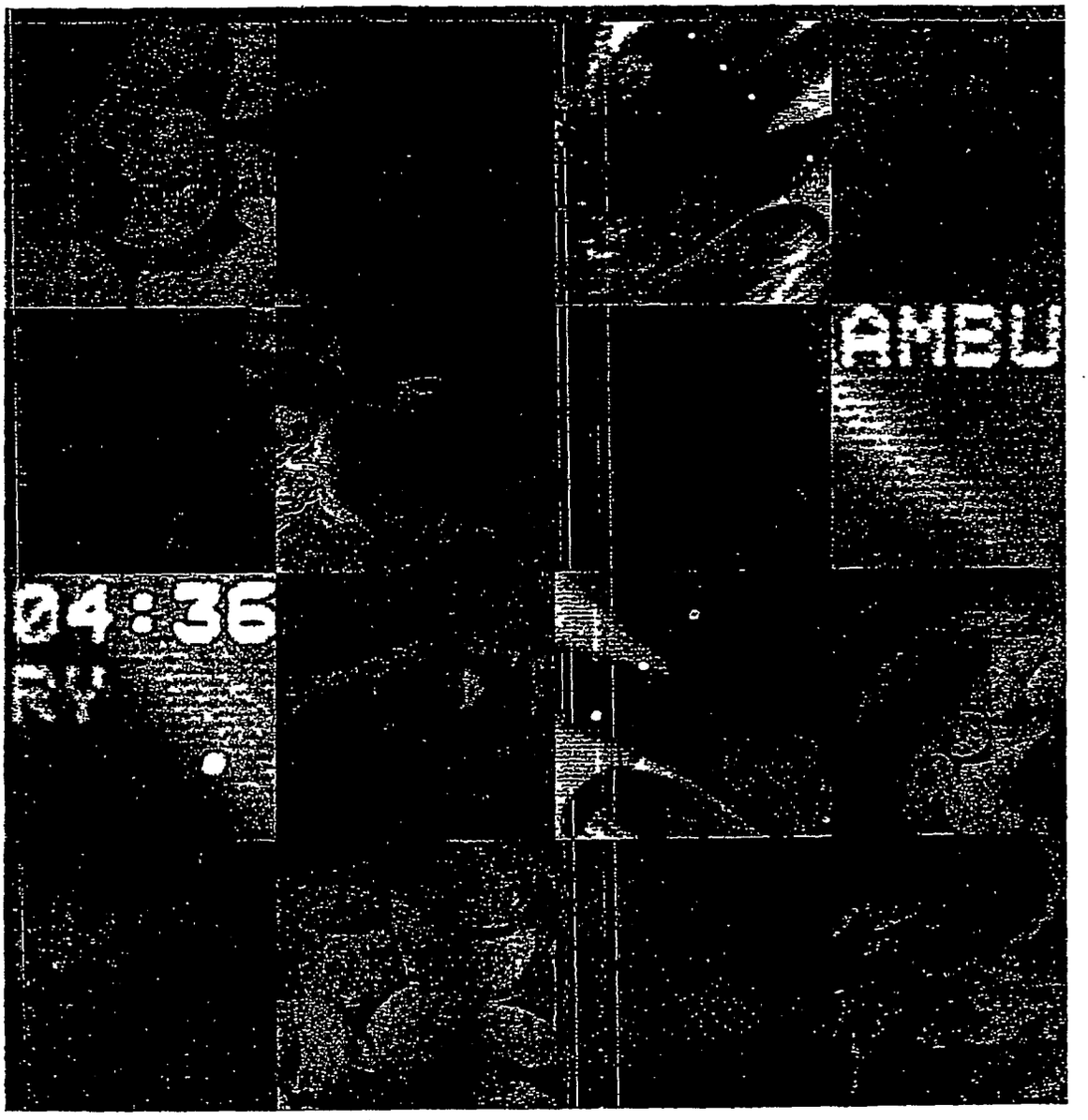
To note Appendix I (fieldwork documents) and the multi-country computer tabulations, that are referred to in the report, are quite lengthy and, as such, were not included with the report but are available upon request In the near future, this information will also be available on the NA Marketing Research intranet site (password protected)

In addition to the report itself, a computer simulation of the product features studied was developed to allow for further analysis

Please feel free to call me at 847 940-5956 should you have questions regarding the study or the associated deliverables

Recombinant Factor VIII positioning study

Multi-country report
June 2000



NOP Healthcare

Recombinant Factor VIII positioning study

Multi-country report

Prepared for Baxter Hyland Immuno

J 500398

June 2000

CONTENTS

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APPENDICES

J500398
EM/MP/SB
12th June 2000

Introduction

Baxter's Hyland Immuno division currently markets several products for the treatment of haemophilia A, including Recombinate

The Factor VIII market comprises human plasma-derived products and the more recently introduced genetically engineered recombinant products (based on recombinant DNA technology) Recombinate is a dominant player in this market

Recombinate and the other recombinant Factor VIII (rFVIII) products currently available contain (human) albumin, which is added to the Factor VIII protein in the final stage of production in order to stabilise the product Furthermore the cell culture medium used in the preparation of rFVIII products also contains albumin This poses the theoretical risk of viral contamination and manufacturers are currently developing protein free rFVIII products

Baxter's research and development is directed towards a completely protein free rFVIII and the company has a potential product in the early phases of clinical trials However, Genetics Institute and Bayer are also known to be developing completely protein free rFVIII products

Baxter now faces the challenge of maintaining its dominant place in this evolving market until such time as its new protein free product is launched Both Genetics Institute and Bayer will have the benefit of reformulated products (containing albumin) and Baxter is considering several positioning strategies to counter the threat posed by these new products These strategies are

1 ***Reduced volume infusions***

The volume of a Recombinate infusion is currently 10 ml, while that of its competitors is 2 5 ml and 5 ml Baxter may wish to reduce the Recombinate infusion volume It is advisable to determine the optimal volume and what reduction in volume is considered sufficiently significant to affect product choice

2 ***Higher potency***

A possibility being considered is to extend the licence for Recombinate in the future to include a potent dosage of 1,500 or 2,000 i u (the highest potency dose for current rFVIII products is 1,240 i u) This dose would better accommodate therapy for adults (a large adult can have up to 2,500 i u)

3 ***Continuous infusion indication***

Another possible product licence extension wou d be to include an indication for continuous infusion Currently none of the rFV II products are licensed for this indication and because of this, there is believed to be some resistance amongst pharmacists to mix rFVIII into an i v bag for con inuous infusion It is estimated that some 10% to 15% of rFVIII usage is used n continuous infusions (for pre- and post-surgical use) and it is not known whether or not the new reformulated products will have this indication

4 ***Novel reconstitution device***

A novel device is being considered for safer, fas er, easier and more convenient reconstitution and administration of Recombinate a needleless device, possi y allowing for multi-vial doses)

In addition, there are a number of other factors hat may influence the use of specific rFVIII products, including

- Human protein - whether used in both mar ufacturing and stabilising, in manufacturing only (reformulated products) or no used at all
- Assay requirements – whether the commonly sed one-stage assay can be used or if a chromogenic assay is required (reformulated products)
- Room temperature storage – whether the rFVIII p roduct requires refrigeration or if it can be stored at room temperature If room temperature is applicable, the shelf life of the product may vary from 3 months to 2 years
- Molecule type – full length rFVIII or B-domain deleted rFVIII

Baxter commissioned NOP Healthcare to conduct a trade-off study in the USA, Japan and Europe, to assist in the development of a positioning strategy for Recombinate and the next generation rFVIII products

Objectives

1. Primary objective

The primary objective of this study was to provide an indication of the relative importance of the various rFVIII product features and the selected levels within each feature

The relative importance of these features and levels was measured independently for the three groups of respondents - physicians, nurses and patients

2. Secondary objectives

The secondary objectives of this study were to establish the following

The breakdown of haemophilia patients by

- types A and B

The breakdown of haemophilia A patients by

- adult and paediatric,
- severity of condition,
- length of time since diagnosis

Patterns of Factor VIII usage

- purpose of treatment – prophylaxis or on demand,
- use of portacaths,
- use of recombinant versus human plasma-derived products
- use of specific brands,
- factors influencing the choice of Factor VIII treatment.

Management summary

1. Relative importance of product features

The trade-off exercise in this study was designed to assess both the relative importance of various product features as well as the varying levels within each feature. Of the eight product features selected by Baxter to be included in the exercise:

i. Reducing/eliminating human protein is the most important feature (eliminating is significantly better)
ii. Capability for continuous infusion is the second most important feature for physicians and nurses (label indication not particularly important)
iii. Room temperature storage is the third most important feature (significant improvement if it does not require refrigeration, stepped improvement with shelf life)
iv. Reconstitution is of some importance for nurses and patients (needleless system and single step procedure)
v. Assay issue is not particularly important for physicians and nurses (but one-stage preferable)
vi. Higher potency product is not particularly sought after (but 1,500 i.u. or 2,000 i.u. preferable)
vii. Diluent volume is unimportant (but smaller volumes preferable)
viii. rFVIII molecule is unimportant for physicians

2. Breakdown of haemophilia patients

i. Approximately four out of five patients are haemophilia type A
ii. Just over half are adults
iii. Approximately half of the haemophilia A patients (USA and Japan) are classified as having a severe condition, and one quarter as having moderate and mild conditions respectively

3 Patterns of Factor VIII usage

I Factor VIII is used predominantly as prophylaxis among paediatrics but more on an 'as needed' basis among adults

II Portacaths are used by less than one in ten adult sufferers, but by almost one-third of children

III On average, rFVIII is being prescribed for around two-thirds of patients and around one-third are being prescribed human plasma-derived products

IV The most common influences on choice of treatment are safety, efficacy, supply and cost

4 Patterns of recombinant Factor VIII usage

I The average length of time that patients have been using rFVIII is eight years for adults and four years for children

II The majority of patients are fairly to very satisfied with the rFVIII products currently available, the main reason for patient satisfaction being the efficacy of the products

III Recombinate is the most widely used rFVIII product followed by Kogenate

IV In addition to reducing/eliminating human protein the capacity for continuous infusion and room temperature storage, rFVIII users also want to see reduced cost, longer half-life and improved safety

Patterns of recombinant Factor VIII usage

- length of time rFVIII products have been used,
- level of satisfaction with currently available products,
- reasons for satisfaction/dissatisfaction,
- desired improvements to currently available products

The preferred rFVIII product (conjoint task)

- reasons for ranking chosen product first,
- level of interest in using chosen product,
- willingness to pay a price premium for selected product.

Research method

Design

To establish the relative importance of the various product features and the levels within each feature, a full profile conjoint technique was incorporated into the design of the research

The following attribute battery (and levels within each attribute) was used

1 *Human protein*

i) used in manufacturing and stabilising (final formulation

ii) used in manufacturing (culturing), but not in the final formulation (for stabilising)

iii) not used at all

This attribute was included in the tasks for doctors, nurses and patients

2 *Continuous infusion*

i) an approved indication

ii) product has capability, but not approved (label indication

iii) not possible

This attribute was included in the tasks for doctors and nurses only

3 *Diluent volume*

i) 2 5ml

ii) 5ml

iii) 10ml

This attribute was included in the tasks for doctors nurses and patients

4 *High potency*

i) 1,000 i u

ii) 1,250 i u

iii) 1,500 i u

iv) 2,000 i u

This attribute was included in the tasks for doctors, nurses and patients

5 **Assay issue**

i) requires one-stage assay

ii) requires chromogenic assay (not available in every hospital)

This attribute was included in the tasks for doctors and nurses

6 *Room temperature storage*

i) Cannot be stored at room temperature (requires refrigeration)

ii) 3 months

iii) 6 months

iv) 1 year

v) 2+ years

This attribute was included in the tasks for doctors, nurses and patients

7 *Reconstitution*

i) current standard (two vials)

ii) current standard, with needleless reconstitution/mixing

iii) single step procedure (i e pre-filled, ready-to-use syringe)

This attribute was included in the tasks for nurses and patients only

8 *rFVIII molecule*

i) full length

ii) B-domain deleted

This attribute was included in the tasks for doctors only

These attributes and levels were incorporated into a 32 card (for doctors and nurses) or 25 card (for patients) orthogonal design for a full profile conjoint task. The resulting utility values provided an indication of the relative importance of each attribute and each level within each attribute

Sample

Haematologists and nurses were recruited and screened to ensure that

- they worked at or were affiliated with a specialist/comprehensive haemophilia treatment centre,
- they specialised in the treatment of haemophilia/bleeding disorders,
- they were involved specifically in the treatment of haemophilia A

Additionally, they were screened to ensure that

- the haematologists were prescribing rFVIII products in the treatment of haemophilia A,
- the nurses were regularly involved in the reconstitution and administration of rFVIII products for treating haemophilia A.

Haematologists in Europe were only recruited if they were treating five or more haemophilia A patients

Patient respondents were screened to ensure that

- either they personally suffered from haemophilia A or had a child suffering from the condition,
- that the haemophilia A sufferer was using a rFVIII product to treat their condition

Quotas were imposed in each country to ensure that the patient group included a significant proportion of paediatric patients, who are more commonly prescribed rFVIII The target quotas were 66% paediatric and 33% adult patients

Baxter withdrew one country (Germany) from the study and it was not possible to meet the quotas in either Japan or Denmark This was because of the small number of haemophilia centres in Denmark, and due to the social stigma associated with haemophilia in Japan

As a result, more doctors and patients were recruited in the USA to assist in reaching the target quotas for each respondent group

The resulting sample totalled 333 respondents, and included 99 haematologists 62 nurses and 172 haemophilia A patients who were receiving rFVIII products. The sample breakdown is shown in the following table

Country	Doctors	Nurses	Patients	Tota
Italy	10	-	20	30
France	10	-	20	30
UK	10	10	22	42
Spain	5	-	10	15
Sweden	5	5	10	20
Denmark	4	2	6	12
			Sub total for Europe	149
Japan	5	5	4	14
USA	50	40	80	170
Total	**99**	**62**	**172**	**333**

Further demographics of the sample groups can be found in the section entitled Demographics

Fieldwork

Fieldwork was undertaken during December 1999 and January 2000 A series of face-to-face interviews were carried out with haematologists, nurses and patients in the USA, Japan and Europe Copies of all fieldwork documents can be found in Appendix I

Data analysis

A copy of the multi-country computer tabulations produced from the results of the screening and main questionnaires (including demographics), can be found in the bound computer tabulations for each respondent group A summary of this information is detailed within the main findings of this report

Separate multi-variate analyses were run for each of the three groups of respondents based on the results of the conjoint task A summary of the findings can be found in the main findings section of the report. The statistical analyses of the conjoint results can be found in Appendix II

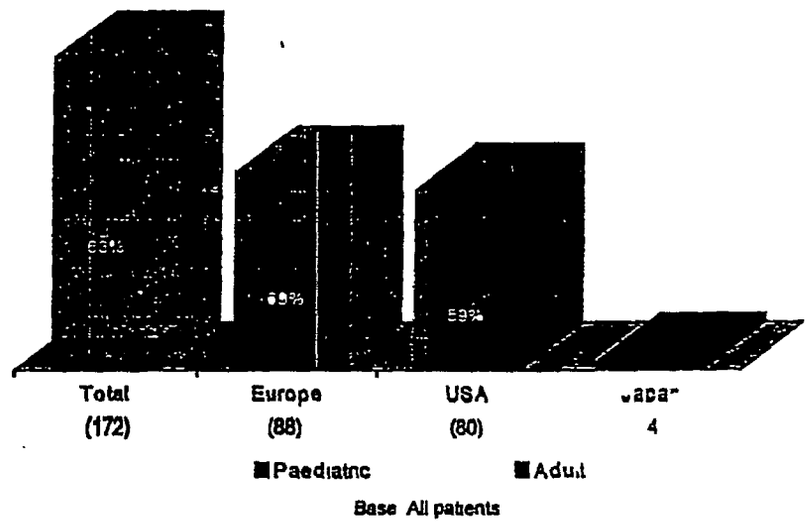
Demographics

1. Type of patient respondent

1 1 Adult/paediatric

As per the target quota, nearly two-thirds of the patient respondent group were parents of children with haemophilia A, except in Japan where only four patients could be recruited for this study and all four were adults and in Denmark where all six recruited patients were children

Type of haemophilia A patient Adult/paediatric

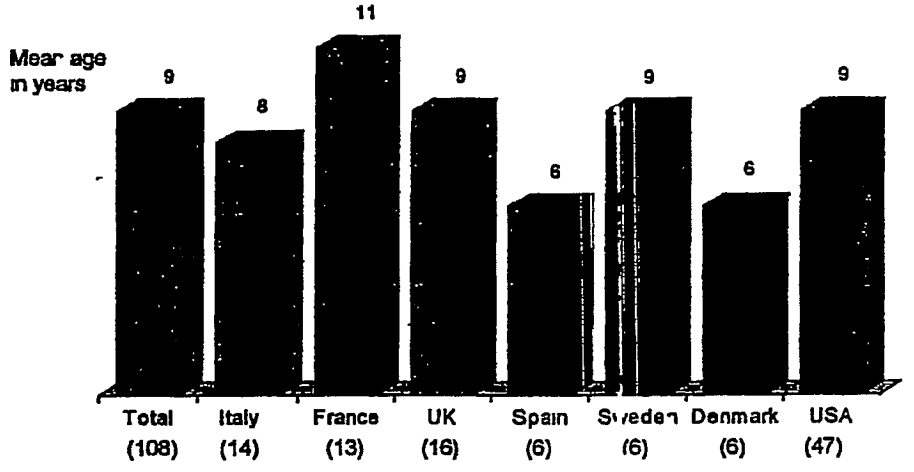


Base All patients

1 2 *Age of paediatric patients*

The mean age of the child sufferers of haemophilia A was nine years This was similar across all countries except Spain and Denmark where the mean age was younger at six years, and in France where the mean age was slightly older at 11 years

Mean age of paediatric patients

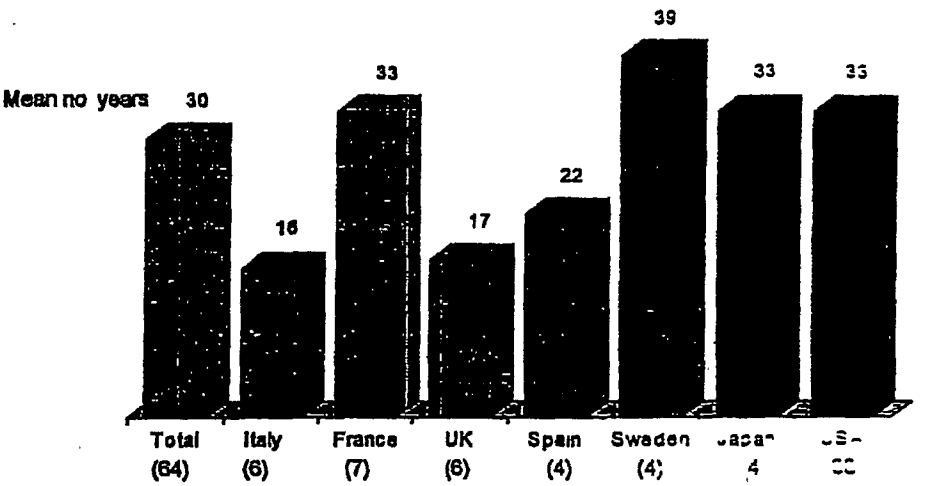


Base All paediatric patients

1 3 *Length of time since diagnosis*

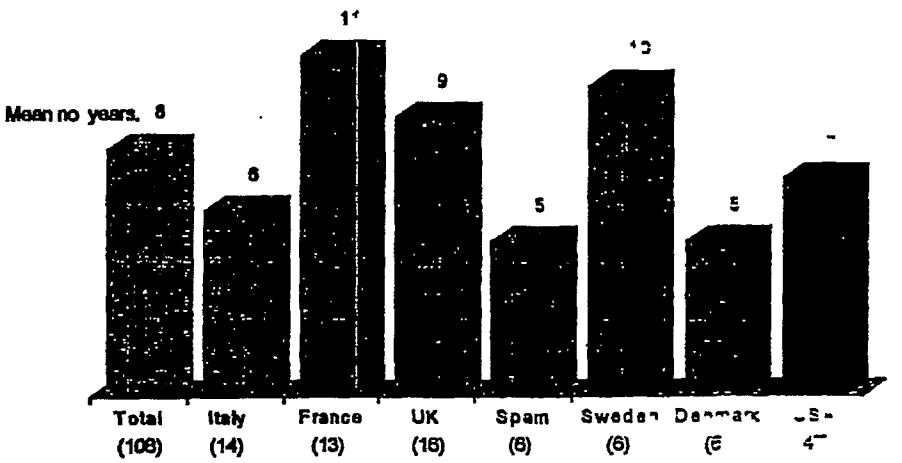
The mean length of time since diagnosis was 30 years for adult sufferers and eight years for child sufferers

Length of time since adult was diagnosed with haemophilia A



Base All adult patients

Length of time since child was diagnosed with haemophilia A



Base All paediatric patients

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iii Approximately half of the haemophilia A patients (USA and Japan) are classified as having a severe condition, and one quarter as having moderate and mild conditions respectively

Main Findings

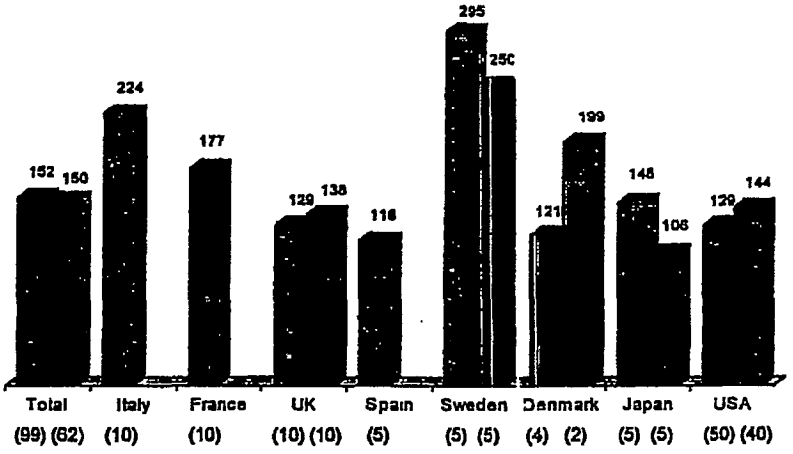
NOP Healthcare

MAIN FINDINGS

1 Haemophilia patient workload

The number of haemophilia patients treated in each centre varied widely across the eight countries, with estimates ranging from eight to 700 The mean number of patients treated was around 150 per centre

Mean number of haemophilia patients treated in each centre



Base All physicians and all nurses

In Japan and the USA, the physicians were also asked how many haemophilia patients they were personally responsible for treating In Japan, the mean number of patients was 148, and in the USA the mean number was 127 In Japan this figure equated to the mean number of haemophilia patients treated in each centre, and in the USA this figure was just under the mean number of haemophilia patients treated in each centre This would appear to indicate that all the physicians in Japan and the majority in the USA were personally responsible for every haemophilia patient treated in the centre in which they worked One physician in the USA stated that s/he was not personally responsible for any haemophilia patients and that the responsibility was shared among physicians

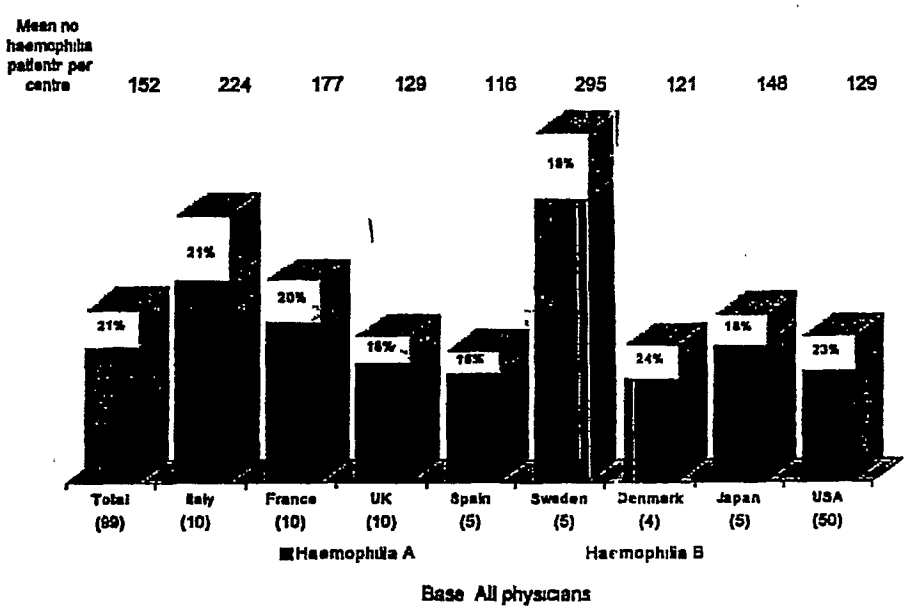
Nurses in Japan and the USA were asked what number of haemophilia A patients would be seen by them in a typical week The mean number was around nine with Japanese nurses seeing on average two more patients in a typical week than nurses in the USA

2. Haemophilia patient types

2.1 Haemophilia type A/B

The estimated percentage of haemophilia patients that were types A and B were very similar across countries. Out of the total number of haemophilia patients treated by physicians, around four-fifths (79%) were said to have haemophilia type A and the remaining fifth (21%) haemophilia type B.

Mean percentage of haemophilia patients with haemophilia type A/B

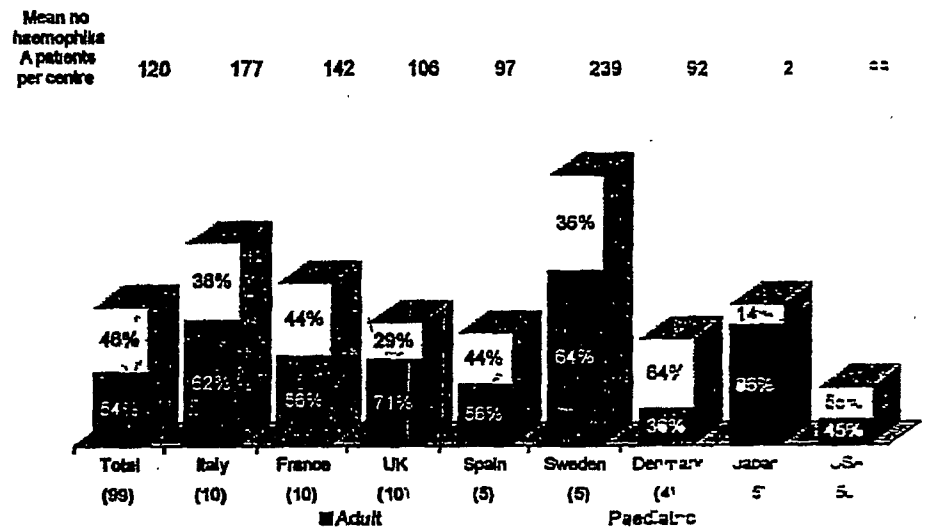


Base: All physicians

2.2 Adult/paediatric patients

There was a wide variation in the centres' proportions of adult and paediatric haemophilia A patients However the means for both the physician and the nurse respondent groups indicated that just over half of the patients treated were adult and just under half were paediatric

Mean percentage of haemophilia A patients who were adult/paediatric

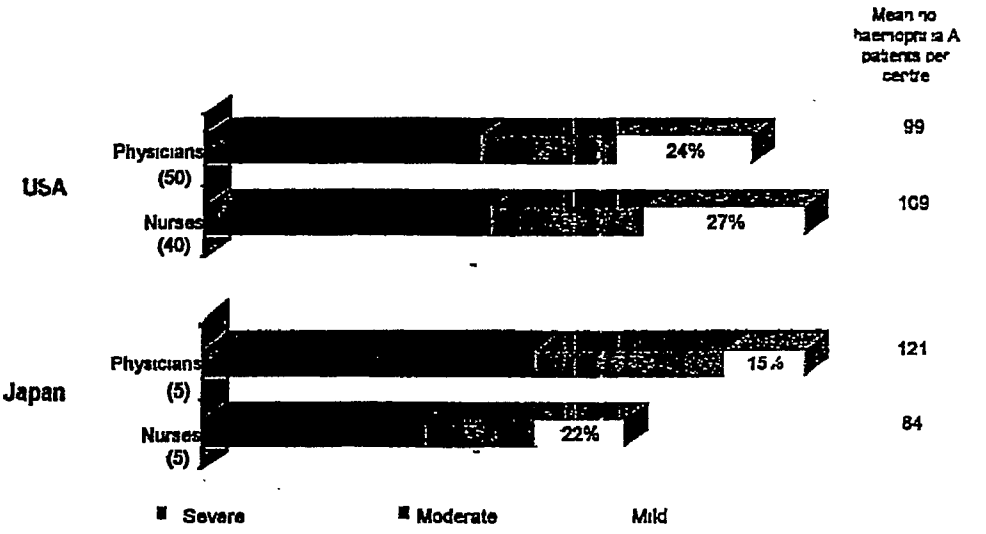


Base: All physicians

2 3 Severity of condition

Nurses and physicians in Japan and the USA were asked to classify their haemophilia A patients by the severity of their condition The results were very similar, with physicians and nurses in both countries estimating that around half of their patients had a severe condition The remaining half were fairly evenly split between mild and moderate forms of the condition

Haemophilia A patients classified by severity of condition



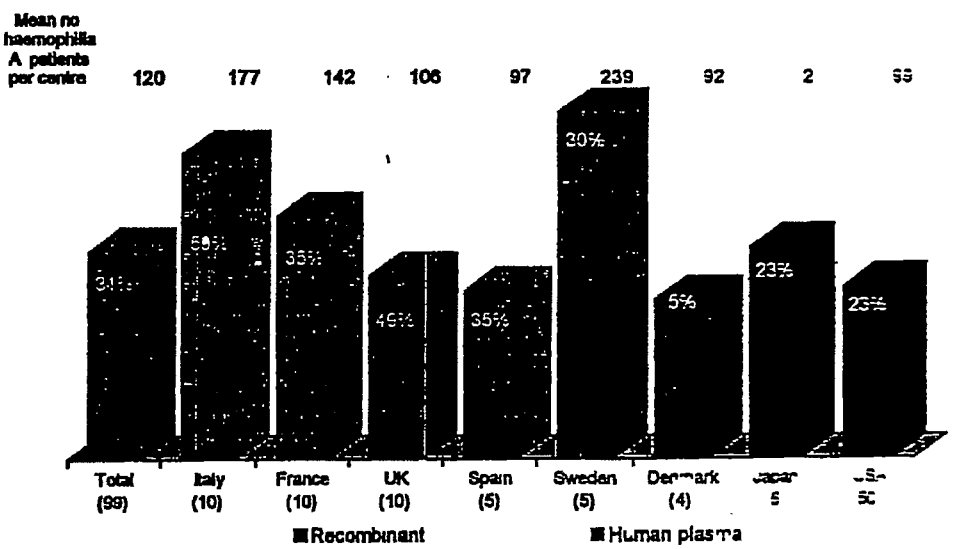
Base All physicians and nurses in USA and Japan

3. Factor VIII usage

3.1 Plasma/recombinant Factor VIII usage

The physicians interviewed estimated that they were prescribing recombinant Factor VIII products, as opposed to human plasma-derived products for around two-thirds (69%) of their haemophilia A patients The nurses' estimates were very similar The highest usage of recombinant products was in Denmark where almost all patients were said to be prescribed recombinant Factor VIII

Mean percentage of patients for whom physicians prescribe recombinant/human plasma Factor VIII

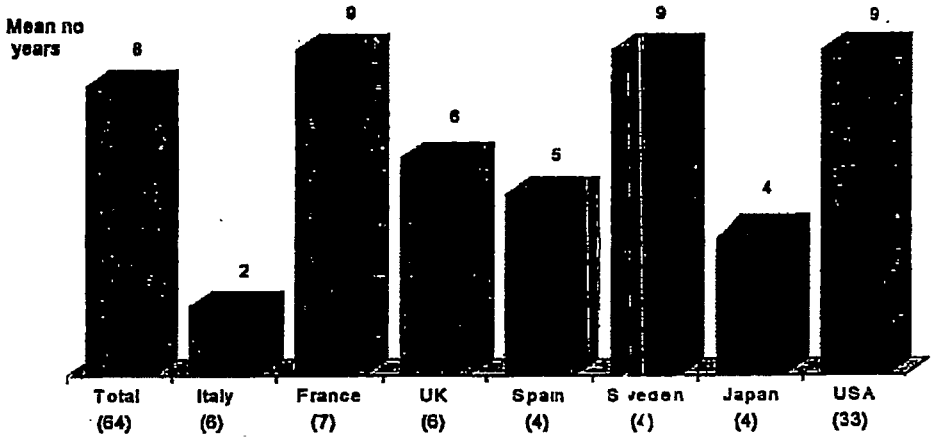


Base All physicians

3 2 Duration of recombinant Factor VIII usage

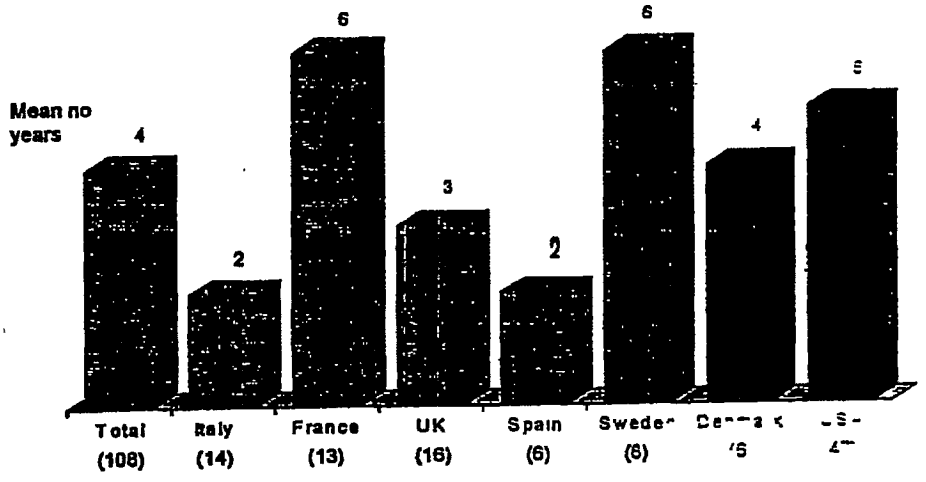
Among the patient respondents, the average length of time that rFVIII products had been used was eight years for adults and four years for children In both adults and children, patients in France, Sweden and the USA had been using the recombinant products for the longest periods of time Conversely in Italy, Spain and Japan, the patients had been using recombinant products for the shortest length of time

Length of time adults had been using recombinant Factor VIII



Base All adult patients

Length of time children had been using recombinant Factor VIII

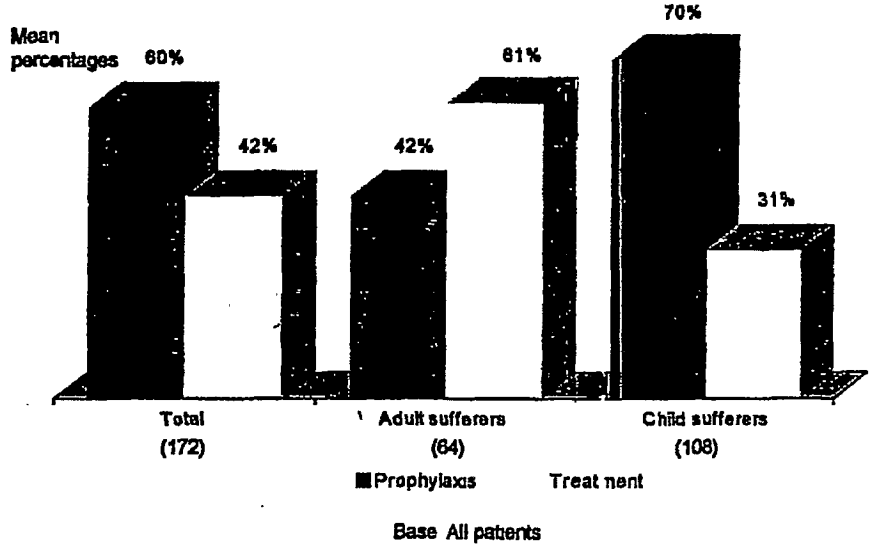


Base All paediatric patients

3 3 Recombinant Factor VIII usage for prophylaxis/treatment

Recombinant Factor VIII was predominantly used as prophylaxis among child sufferers (70%) However, adults tended to use it more on an "as needed" basis (61%) rather than as a preventative measure

Use of recombinant Factor VIII as prophylaxis/treatment



Base All patients

The following table illustrates the usage patterns by country

Country		Prophylaxis	On demand
Italy	Adult (6)	3 (50%)	3 (50%
	Child (14)	4 (29%)	10 (71%
France	Adult (7)	3 (43%)	4 (57%
	Child (13)**	8 (62%)	5 (38%
UK	Adult (6)	5 (83%)	1 (17%
	Child (16)	15 (94%)	1 (6%
Spain	Adult (4)	1 (25%)	3 (75%
	Child (6)*	4 (67%)	1 (17%
Sweden	Adult (4)**	4 (100%)	1 (25%
	Child (6)	6 (100%)	-
Denmark	Adult	-	-
	Child (6)	5 (83%)	1 (17%
Japan	Adult (4)	1 (25%)	3 (75%
	Child	-	-
USA	Adult (33)**	10 (30%)	24 (73%
	Child (47)**	34 (72%)	14 (30%
Total	Adult (64)	27 (42%)	39 (61%)
	Child (108)	76 (70%)	34 (31%)

*One respondent stated "don't know"
**These groups included a small number of patients who used FVIII both as prophylaxis and on-demand

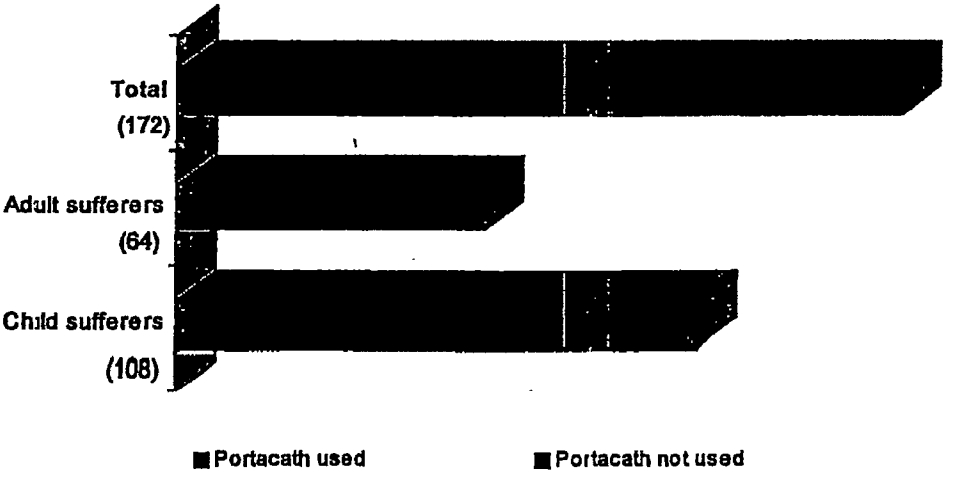
- Interestingly in Italy where almost three-quarters of the patient respondents were children with haemophilia A, just under one third of Factor VIII usage was for the purpose of prophylaxis, while in just over two-thirds of child respondents it was used on an "as needed" basis,

- All patients in Sweden and most in the UK and Denmark used rFVIII products as prophylaxis,
- rFVIII was most commonly used on an "as needed" basis among adult patients in Spain, Japan and the USA

3 4 Use of portacaths for delivering recombinant FVIII

Not surprisingly, portacath use was more common among paediatric patients than adults, with almost one third of children (30%), but less than one in ten adults, using portacaths for the delivery of rFVIII

Use of a portacath (catheter) for the administration of rFVIII



Base All patients

The following table shows a breakdown of portacath use by country

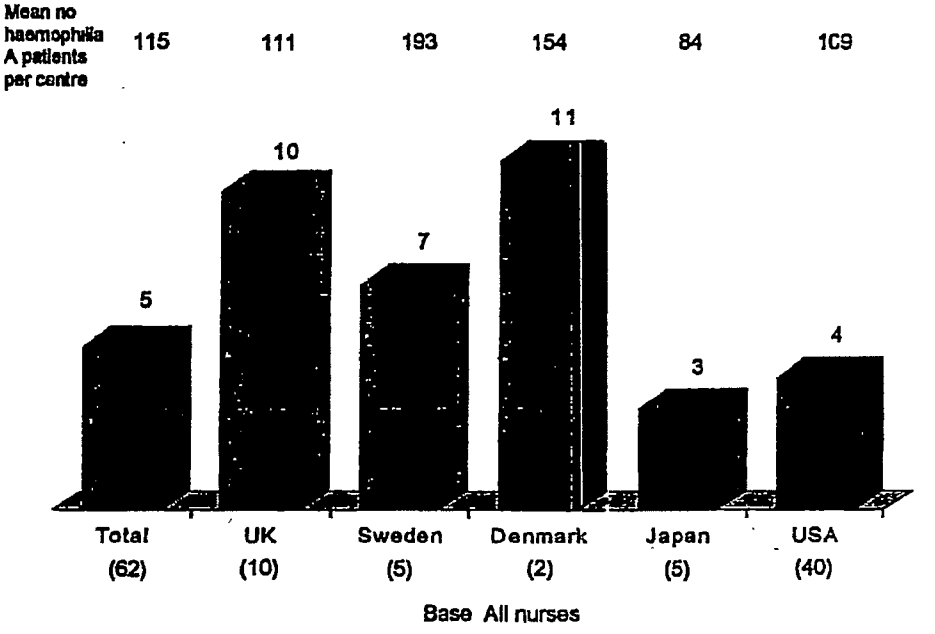
Country		Portacath used	Portacath not used
Italy	Adult (6)	1 (17%)	5 (83%)
	Child (14)	-	14 (100%)
France	Adult (7)	-	7 (100%)
	Child (13)	2 (15%)	11 (85%)
UK	Adult (6)	1 (17%)	5 (83%)
	Child (16)	5 (31%)	11 (69%)
Spain	Adult (4)	-	4 (100%)
	Child (6)	1 (17%)	5 (83%)
Denmark	Adult	-	-
	Child (6)	3 (50%)	3 (50%)
Sweden	Adult (4)	-	4 (100%)
	Child (6)	3 (50%)	3 (50%)
Japan	Adult (4)	1 (25%)	3 (75%)
	Child	-	-
USA	Adult (33)	3 (9%)	30 (91%)
	Child (47)	18 (38%)	29 (62%)
Total	**Adult (64)**	**6 (9%)**	**58 (91%)**
	Child (108)	**32 (30%)**	**76 (70%)**

- Half the children in Denmark and Sweden were using portacaths for the delivery of rFVIII,
- None of the children in Italy were using portacaths

3 5 In-centre administration of recombinant Factor VIII

The mean number of occasions that nurses reconst tuted and/or administered rFVIII products in a typical week was five, however this igure was double for nurses in Denmark and the UK There was no apparent cor elation between the number of patients managed by the centre and the number of times nurses administered rFVIII

Mean number of times rFVIII was reconstituted/administered per week



There was no difference in administration/reconstitu tion patterns between centres that had mainly paediatric patients (>50%) and those that managed more adults (>50%) than children, with the mean being five in both types of centres

3.6 Most widely used Factor VIII products

The Factor VIII products most commonly used by the physicians and nurses interviewed are listed in the following summary table

% of physicians using specified product

Product	Physicians (99)	Nurses (62
Recombinant		
Recombinate	91%	84
Kogenate	76%	82
Helixate	55%	48
Refacto	28%	3
Bioclate	26%	03
Human plasma		
Haemate P/Humate-P	35%	02
Hemofil M	32%	02
Monoclate-P	27%	02
Alphanate	24%	16
Monarc M	10%	10
Emoclot	10%	-
Koate DVI	6%	13
Octnativ M	3%	10

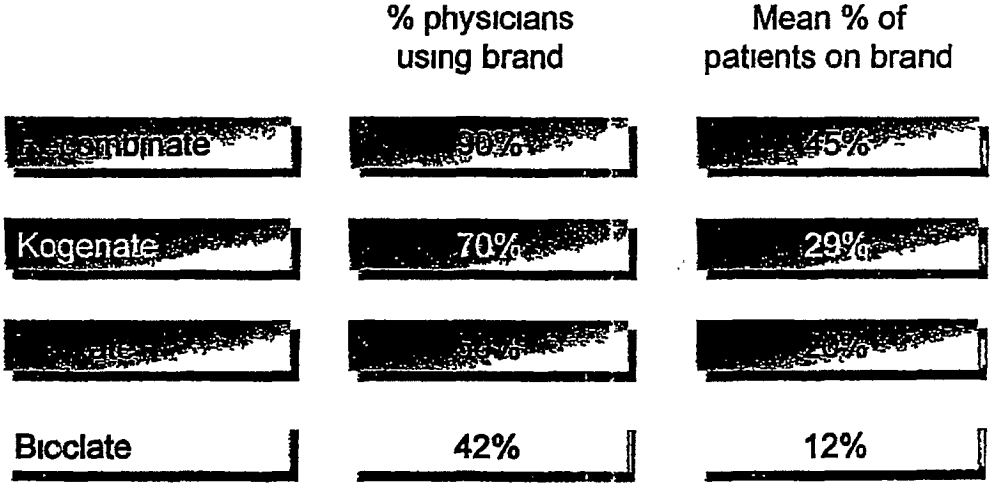
- Recombinate was the most commonly used rFVIII product in all countries
- Haemate P/Humate-P was the only human plasma-derived product used by physicians and nurses in all countries (except Japan),
- among physicians, human plasma-derived products were used by more physicians in Italy than in any other country This correlates with the data

section 3 1, which shows that physicians ir Italy were prescribing human plasma-derived products for 59% of their pat ents whereas the mean for all countries was 31% A full breakdown by coun ry can be found in the computer tabulations that accompany this report.

3 7 Most widely used rFVIII products (USA a id Japan)

In the USA, Recombinate was the most common y used rFVIII product, used by 90% of the physicians for an average of 45% of the r patients

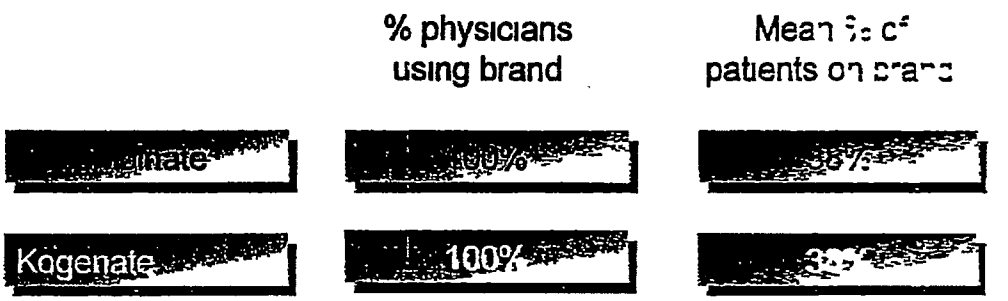
Usage of specified brands of recombinant Factor VIII in the USA



Base All physicians in the USA (50)

In Japan, both Recombinate and Kogenate were used by all the physicians interviewed in this study

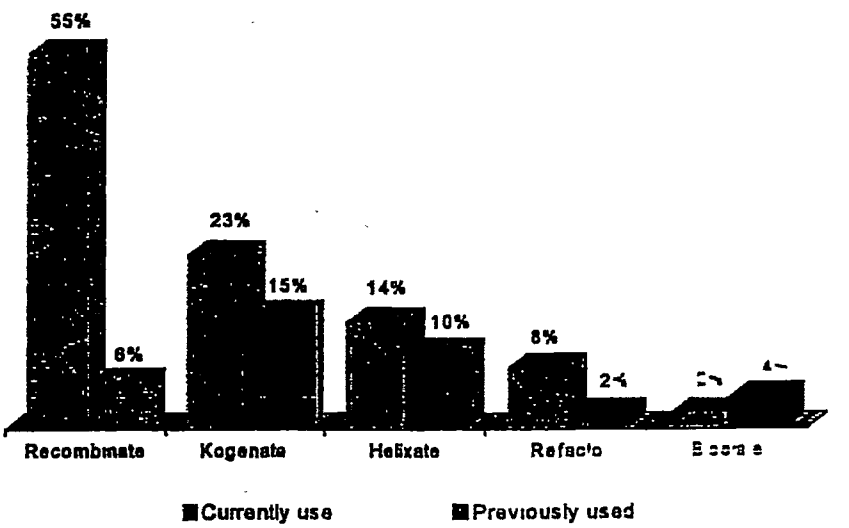
Usage of specified brands of recombinant Factor VIII in Japan



Base All physicians in Japan (5)

The patient interviews confirmed the dominant position of Recombinate in the rFVIII market The following chart indicates the brands of rFVIII currently and previously used by the patients interviewed in this study

Mean percentage of patients using specified brands of rFVIII



Base All patients (172)